

**Efforts Toward the Synthesis of Taxane
Natural Products**

A thesis presented

by

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to

The Department of Chemistry
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy

at the

Massachusetts Institute of Technology

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Efforts Toward the Synthesis of Taxane Natural Products

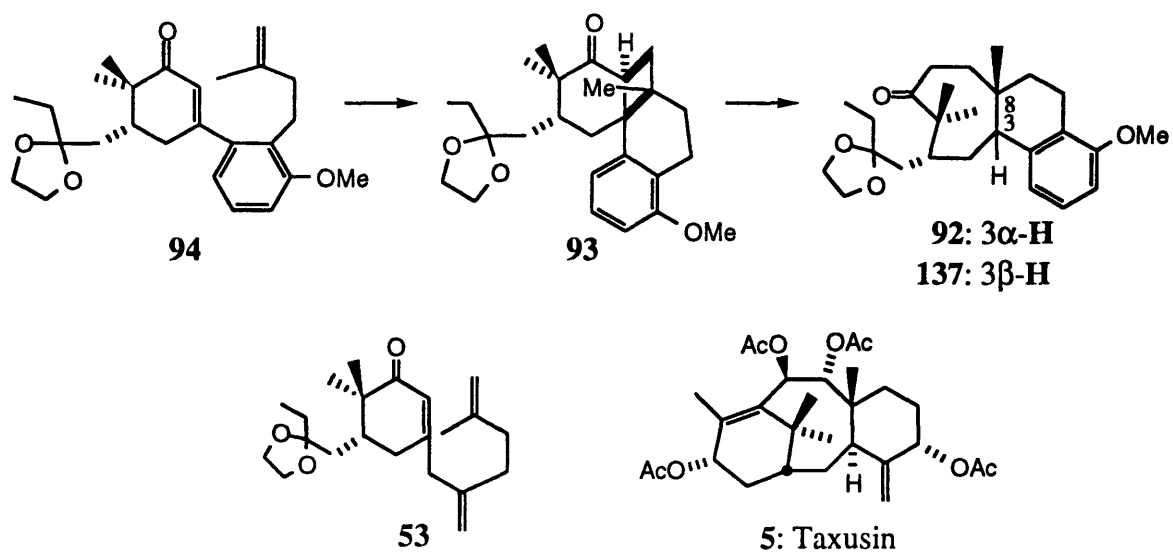
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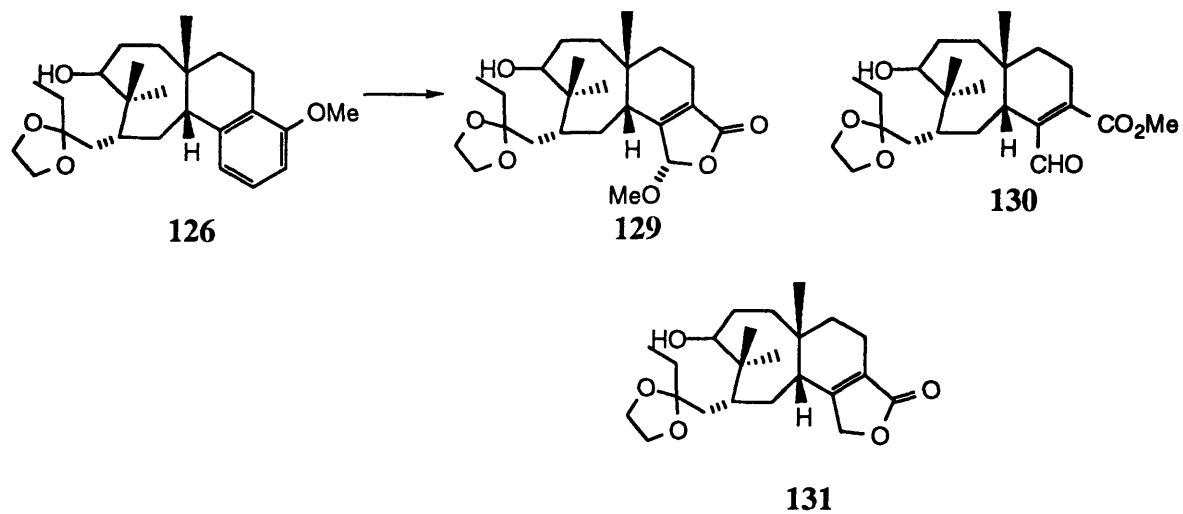
Submitted to the Department of Chemistry
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Chemistry at the Massachusetts Institute of
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ABSTRACT

Studies for this thesis involve efforts toward the enantioselective total synthesis of taxusin (5). Key features of the synthetic sequence include a diastereoselective, intramolecular enone-olefin [2+2] photocyclization of photosubstrate **94** which introduces the correct stereochemistry of the C(8) methyl group. This reaction represents an unprecedented total reversal of stereochemistry from the photocyclization of photosubstrate **53** through the substitution of an aromatic ring. Another key feature of this study is the fragmentation of cyclobutane intermediate **93** with lithium and liquid ammonia which results in the selective formation of either cyclooctanone **92** or cyclooctanone **137**, each as a single diastereomer. Cyclooctanone **92**, which incorporates the correct *trans* stereochemistry across the B-C ring juncture of taxusin, is selectively formed by using a nearly stoichiometric amount of lithium in the reaction mixture, while cyclooctanone **137** is obtained selectively by using an excess of lithium in the reaction vessel.



An additional study involves the unique cleavage of the anisole ring of compound **126** with ozone which results in the selective formation of either acetal lactone **129**, ester aldehyde **130**, or lactone **131** depending on solvents and reducing agent used.



Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

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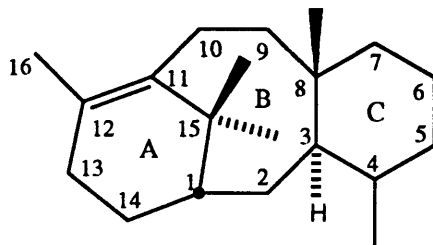
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Chapter 1. Introduction

1.1 Historical Background

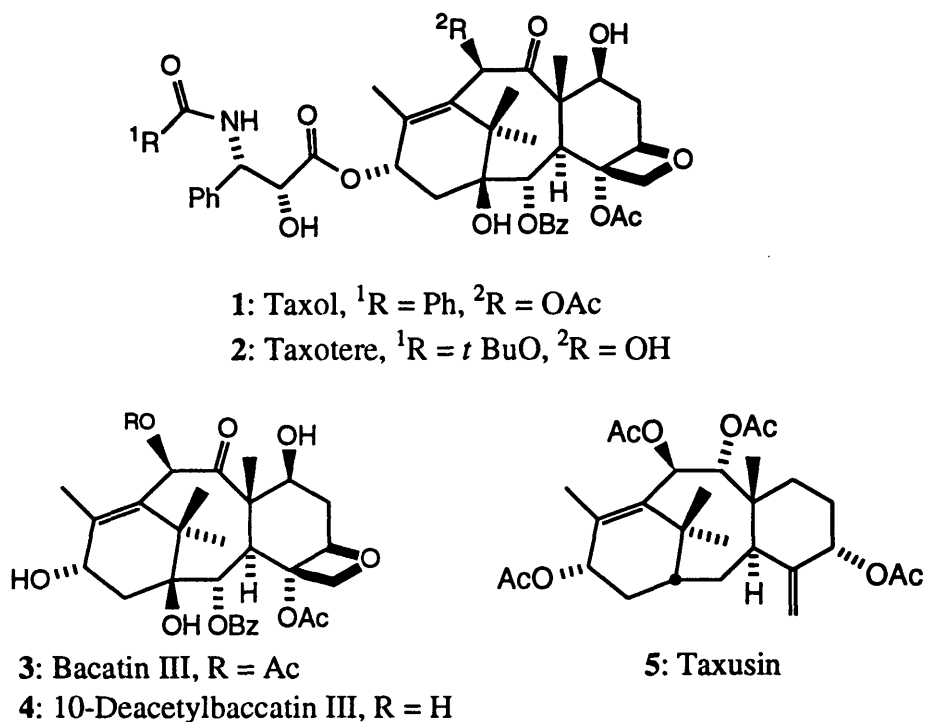
The taxanes¹ are a group of diterpene natural products that are isolated from various yew (*Taxus*) species, and possess the carbon skeleton shown below. These compounds exhibit a wide range of functionality (Scheme 1), culminating with taxol (1), which is the most functionally and stereochemically complex of all of the taxanes.



Much interest has been generated over the past decade in taxol not only for its important antitumor activities, but also because it presents a unique and difficult challenge to the synthetic organic chemist. As demonstrated in Scheme 1, taxol consists of a novel ring system, which incorporates a bridged bicyclo[3.5.1]undecane system as the A-B portion of the molecule, including two complicating functional groups: (1) the bridgehead olefin in the A-ring, and (2) the geminal methyl groups at the C(15) position. The structure also incorporates as the B-C portion of the molecule a *trans*-fused bicyclo[6.4.0]dodecane system, both of which pose considerable synthetic challenges. The molecule also possesses a high degree of sensitive oxygen functionality, and incorporates eleven stereocenters. Because of the many complexities that must be overcome in order to achieve a successful synthesis of taxol, our group, as well as many others, has chosen taxusin

¹(a) Lythgoe, B. *The Alkaloids* 1968, 10, 597. (b) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry," Vol.1, Chapter 4, p. 281, Kodansha -Academic Press, Tokyo, 1974. (c) Miller, R. W. *J. Nat. Prod.* 1980, 43, 425.

(5),² which is the least functionalized member of the taxane family, as a preliminary target through which methodology toward the synthesis of taxol can be developed. As is evident in Scheme 1, taxusin consists of the identical carbocyclic framework as taxol including functionality that could be converted into the oxetane D-ring.



Scheme 1: Selected taxane diterpenoids.

Taxol was first isolated in 1962 from the Pacific yew tree (*Taxus brevifolia*) by Barclay³ who was collecting samples from an Oregon forest due to a widespread search for new antineoplastic agents.⁴ His samples were sent to Research Triangle Park in North Carolina where initial screening suggested that the extracts exhibited potent cytotoxic

²(a) Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Liu, C. L.; Lin, Y. C.; Lin, Y. M.; Chen, F. C. *T'ai-wan K'o Hsueh* **1984**, *38*, 119. (c) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931. (d) Lee, C. L.; Hirose, Y. *Nakatsuka Mokuzai Gakkaishi* **1975**, *21*, 249. (e) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923.

³Junod, T. *Life* **1992**, *15*, 71.

⁴(a) Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622. (b) Driscoll, J. S. *Cancer Treat. Rep.* **1984**, *68*, 63. (c) Marsoni, S.; Wittes, R. *Cancer Treat. Rep.* **1984**, *68*, 77.

activity against leukemia and various tumor cell lines. The active component was isolated and determined to be taxol by Wani and Wall who solved the structure of the molecule, including the absolute stereochemistry, via X-ray crystallographic techniques.⁵

Proceeding the discovery of taxol, interest in the molecule remained low, because taxol was thought to possess the same mechanism of action as two already well known antitumor agents -- vinca alkaloids and colchicine. It was not until 1979 that the mode of action of taxol was determined by Horwitz to be unique.⁶ Both groups, *i.e.* taxol and vinca alkaloids and colchicine, were found to act upon the same organelles in the molecule, the microtubules; however, while vinca alkaloids and colchicine acted to destabilize the microtubules in the cell, taxol was discovered to stabilize them.

The microtubules are important in wide variety of cellular functions and are therefore viewed as one of the most strategic targets in the fight against many types of cancers. They play a central role in the formation of the cytoskeleton,⁷ the transmission of cellular signals,⁸ the organization of organelles,⁹ and the movement of the cell;¹⁰ however, probably the most important activity of the microtubules is their role in mitosis where the microtubules polymerize to form the mitotic spindle. This structure is primarily responsible for the partitioning of the cell's genetic material during anaphase when it is believed that the microtubules depolymerize and therefore cause the separation of the cell's chromosomes.¹¹ Any disruption in the cell's carefully maintained equilibrium during cell division and growth dramatically results in cell death.

⁵Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

⁶Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature*, **1979**, *277*, 665.

⁷Brinkley, B. R. *Cold Springs Harbor Symp. Quant. Biol.* **1982**, *46*, 1029.

⁸Rasenick, M. M.; Wang, N.; Yan, K. *Adv. Second Messenger Phosphoprotein Res.* **1990**, *24*, 381.

⁹Cooper, M. S.; Cornell-Bell, A. H.; Chernjowsky, A.; Dani, J. W.; Smith, S. J. *Cell* **1990**, *61*, 135.

¹⁰Scholey, J. M. *Nature* **1990**, *343*, 118.

¹¹(a) McIntosh, J. R.; Koonce, M. P. *Science* **1989**, *249*, 622. (b) Kuriyama, R.; Nislow, C. *Bioessays* **1992**, *14*, 73. (c) Kirschner, M.; Mitchison, T. *Cell* **1986**, *329*. (d) Saxton, W. M. *J. Cell. Biol.* **1984**, *99*, 2175. (e) McIntosh, J. R.; Pfarr, C. M. *J. Cell Biol.* **1991**, *115*, 577. (f) Gorbisky, G. *Bioessays* **1992**, *14*, 81.

The vinca alkaloids and colchicine are known to act upon the microtubules to destabilize them, causing them to lose their ability to polymerize. This prevents the formation of the mitotic spindle, and consequently the chromosomes are not partitioned correctly. This halts cell division, and cell death is the ultimate result.¹² Oppositely, taxol stabilizes the microtubules, and greatly enhances their assembly. Once polymerized, the microtubules are so stabilized that they are unable to depolymerize at the end of anaphase. This arrests the cell cycle, and results in cell death.¹³

Upon the discovery of the novel mechanism of action possessed by taxol, much interest was generated in the molecule; however, there were small amounts of the drug available for testing due to difficulties in obtaining it from natural resources.¹⁴ This was because the only source that offered taxol in its active form was the bark of the Pacific yew tree, a tree that was slow to mature, and was relatively small. Additionally, the collection of the bark of the Pacific yew threatened the existence of the spotted owl, as the Pacific yew forests were their only natural habitat.¹⁵

The increasing interest in the drug and the need for large amounts for use in clinical trials underscored the importance of finding sources other than natural isolation from the Pacific yew. This need established the urgency of a synthetic route to the molecule, and consequently, in the early 1980's many groups began projects to develop methodology towards its synthesis.¹⁶ In 1988, Holton published the total synthesis of the first member

¹²Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219.

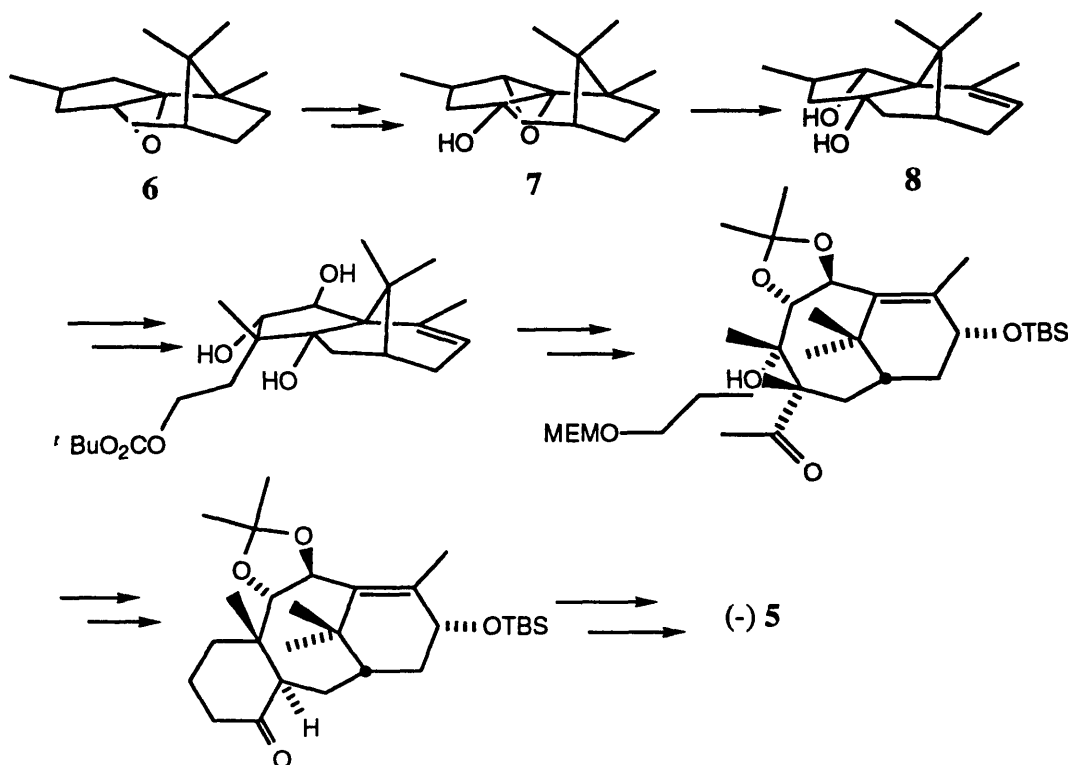
¹³(a) Manfredi, J. J.; Fant, J.; Horwitz, S. B. *Eur. J. Cell Biol.* **1986**, *42*, 126. (b) Solari, A. J.; Duschak, V. G. *Micro Sc. Electron. Biol. Cel.* **1985**, *9*, 163. (c) Bhattacharyya, B.; Ghoschaudhuri, G.; Maity, S.; Biswas, B. B. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 791. (d) Horwitz, S. B.; Lothstein, L.; Manfredi, J. J.; Malcado, W.; Parness, J.; Roy, S. N.; Schiff, P. B.; Sorbara, L.; Zeheb, R. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 733. (e) Wallin, M.; Nordh, J.; Denium, J. *Biochim. Biophys. Acta.* **1986**, *880*, 189.

¹⁴Blume, E. J. *Natl. Cancer Inst.* **1991**, *83*, 1054.

¹⁵(a) Hartzell, H. *The Yew Tree A Thousand Whispers*, Hulogosi, Eugene, OR, USA, **1991**. (b) Bolsinger, C. L.; Jaramillo, A. E. *Silvics of North America: Vol 1., Conifers*, (Eds.; R. M. Burns, B. H. Honkala), USDA: Forest Service Washington, DC, USA, pp. 573.

¹⁶Over 20 different laboratories published articles resulting from studies that were begun at this time. See: (a) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (b) Kraus, G.; Thomas, P. J.; Hon, Y. S.; *J. Chem. Soc., Chem. Commun.* **1987**, 1849. (c) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 221. (d) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (e) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (f) Winkler, J. D.; Hey, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6425 and references cited therein.

of the taxane family, (-)-taxusin, the unnatural isomer of the molecule.¹⁷ His route was a linear strategy that consisted of the AB \rightarrow ABC synthetic plan (Scheme 2), beginning from β -patchoulene oxide (6). The key step of this synthesis was a rearrangement of epoxide 7 to form diol 8 which was converted in 30 steps to *ent*-taxusin.¹⁸



Scheme 2: Holton's synthesis of (-)-taxusin.

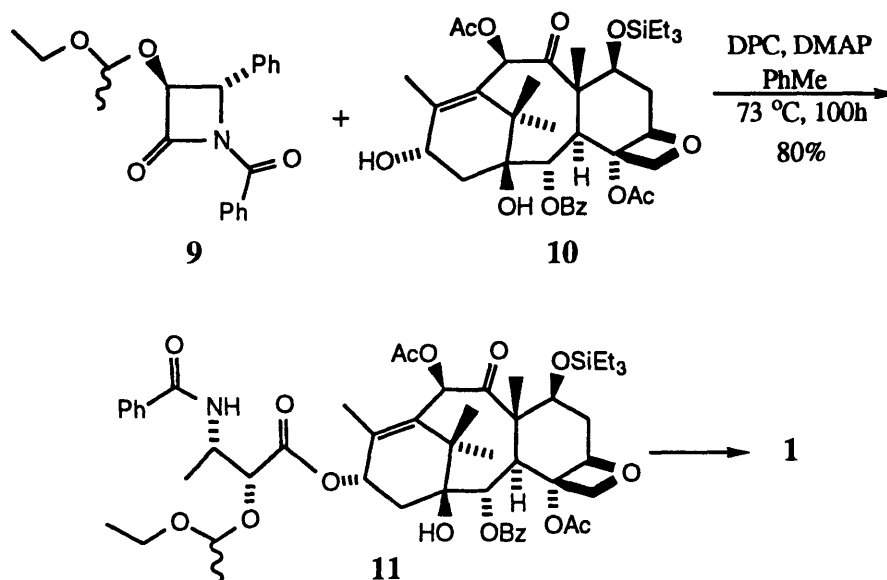
In 1990, Holton and Ojima independently made important discoveries toward solving the shortage problems of taxol through the development of a semisynthesis.¹⁹ They found that active taxol could be formed in five steps from baccatin III (3) through the coupling of side chain derivative 9 to C(7) protected baccatin III (10) which afforded

¹⁷Holton, R. A.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. K.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

¹⁸This is the only total synthesis of taxusin that has been published to date.

¹⁹The first semisynthesis was achieved by Potier and Greene. See: (a) Denis, J. N.; Greene, A. E.; Guénard, D.; Gueritte-Voegelein, F.; Mangatal, P.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. (b) Senilh, V.; Gueritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Seances Acad. Sci. Ser. 2* **1984**, *299*, 1329.

compound **11** (Scheme 3). Compound **11** could then be deprotected in two steps to form natural taxol (**1**).²⁰ This was an exciting finding, as the harvesting of baccatin III, which was isolated from the needles European yew (*Taxus baccata*) in high yields, did not result in the death of the tree.²¹



Scheme 3: Holton and Ojima's semisynthesis of taxol.

Despite the excitement generated in the use of taxol as an anticancer agent, several problems associated with the formulation and toxicity of the drug still exist. Taxol suffers from low water solubility (0.03 mg mL^{-1})²² which forces its formulation in a Cremaphor vehicle, and it also possesses all problems that stem from its cytotoxicity, similar to any other chemotherapeutic drug. However, notwithstanding the inherent problems of the

²⁰(a) Holton, R. A. *Workshop on Taxol and Taxus: Current and Future Prospectives*. National Institute of Cancer, Bethesda, MD 1990. (b) Holton, R. A. *EP-A 400971*, 1990. (c) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.; Jayasinghe, L. R. *J. Org. Chem.* 1991, 56, 6939. (d) Ijima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* 1992, 57, 4320.

²¹Chauviere, G.; Guénard, D.; Picot, F.; Senilh, V.; Potier, P. C. *R. Acad. Sci. Paris* 1981, 293, 501.

²²Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* 1991, 34, 1176.

drug, the FDA approved taxol for the use against drug refractory ovarian cancer in 1993, and continues to perform clinical trials for its use against a variety of other neoplasms.²³

Most recently, 23 years after its discovery, efforts towards the total synthesis of taxol were successful, as Nicolaou²⁴ and Holton²⁵ independently published the first total syntheses of the active molecule.

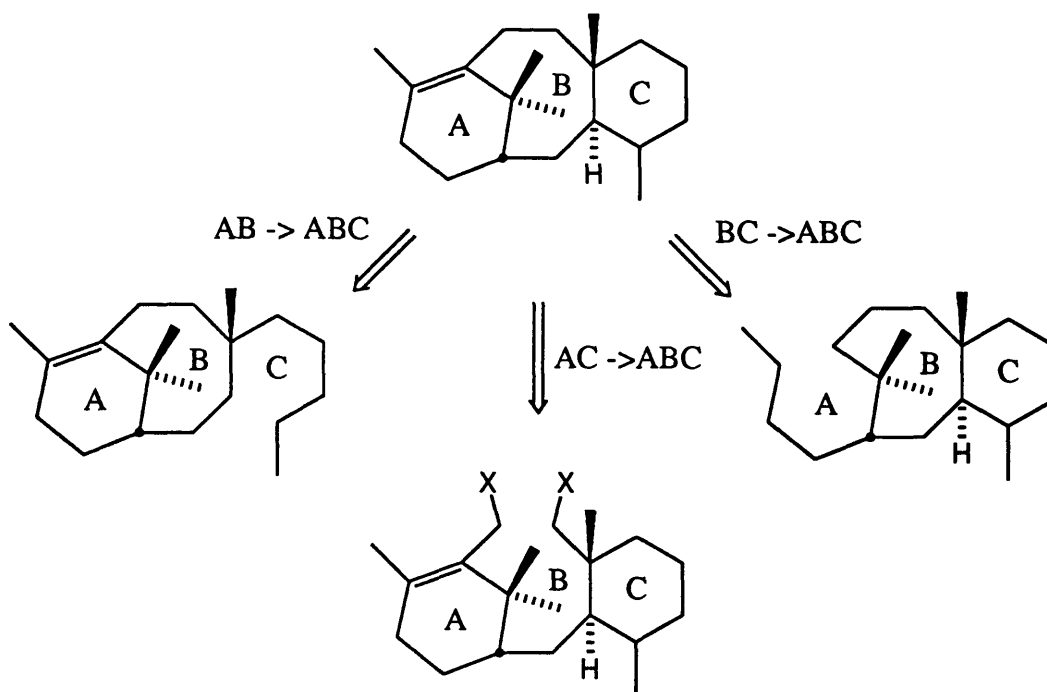
²³*Science* **1993**, *259*, 181.

²⁴Nicolaou, K. C.; Zang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.

²⁵Holton, R. A.; Kim, H. -B.; Somoza, C.; Liang, F.; Biedinger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597.

1.2 A Review of Synthetic Strategies

In designing a synthesis of taxol, one must consider the highly oxygenated nature of the molecule, as well as plan steps that will form the molecule's eleven stereocenters; however, arguably, the most challenging problem facing synthetic chemists is the construction of complex taxane carbocyclic framework. Complicating this problem is the eight-membered B-ring, which is difficult to construct due to the high degree of ring strain and transannular interactions.²⁶ As a result of the unique structural constraints of eight-membered rings, their synthesis is often not possible using conventional annulation strategies such as aldol reactions that are useful toward the synthesis of smaller rings (3-7).



Scheme 4: Disconnections of the taxane framework.

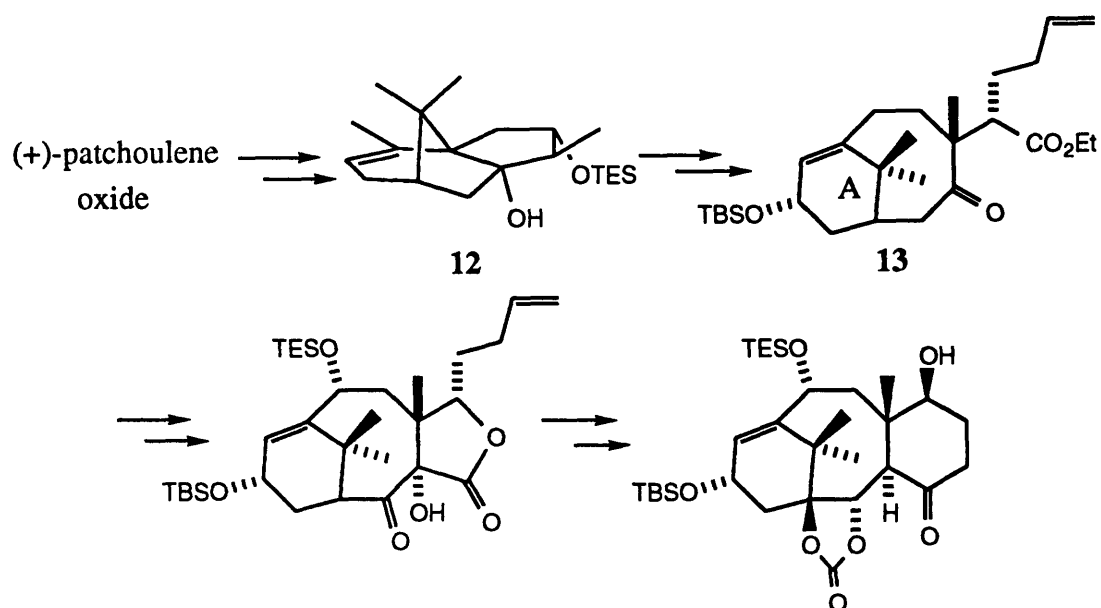
²⁶Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

Because of the problems inherent in the construction of eight-membered rings, the synthetic plan used to form the cyclooctane B-ring in taxol is central to many group's synthetic strategies. Therefore, the order of ring formation is very important to a successful synthesis. A review of ongoing strategic plans for the synthesis of taxanes by Swindell has compiled most of the synthetic approaches of taxanes, and these strategies can be classified according to the order of ring formation in the taxane carbocycle (Scheme 4).²⁷

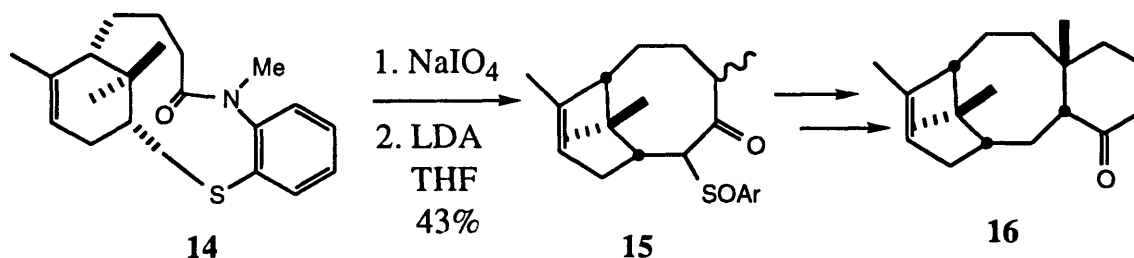
The first of these synthetic strategies is the AB \rightarrow ABC synthetic strategy, and has been widely published in the literature. This strategy is a linear strategy that, in most cases, consists of the construction of an A-B bicycle upon which the C-ring is cyclized. Examples of this strategy are shown in Scheme 5, the first of which has been employed by Holton in his total synthesis of taxol.²⁵ Similar to his synthesis of taxusin, Holton's synthesis of taxol forms A-B bicycle **13** during an early rearrangement reaction of a derivative of patchulene oxide **12**. The C-ring is attached in proceeding reactions. Oishi and Ohtsuka also employ this order of ring formation, with the key step of their synthetic plan being a base-induced ring contraction of sulfoxide **14** to afford A-B bicycle **15**.²⁸ Construction of the C-ring is accomplished in later steps; however, attempts to epimerize tricycle **16** to obtain the correct B-C ring juncture have been unsuccessful.

²⁷Swindell, C. S. *Org. Prep. and Proc. Int.* **1991**, *23*, 465.

²⁸(a) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 443. (b) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 454. (c) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1979**, 4487. (d) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4722. (e) Ohtsuka, Y.; Oishi, T. *Heterocycles* **1984**, *21*, 371. (f) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4722. (g) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203.



Holton's Synthetic Strategy Towards Taxol



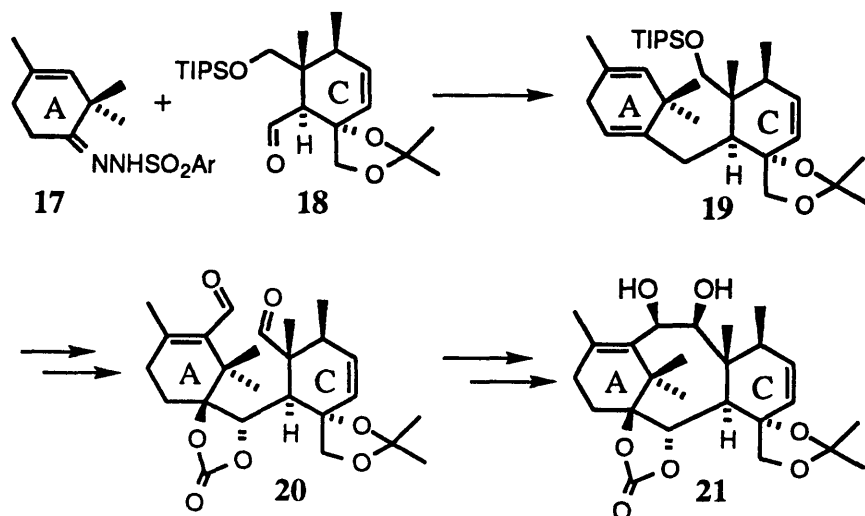
Oishi and Ohtsika's Efforts Towards Taxanes

Scheme 5: Examples of AB- \rightarrow ABC strategy.

Nicolaou, in his 1994 total synthesis of taxol, employed the AC- \rightarrow ABC strategy where the B-ring was the final carbocycle to be constructed (Scheme 6).²⁴ This synthesis was an example of the most convergent of the above synthetic plans. In his synthesis, Nicolaou coupled the A and C ring precursors (17 and 18) through a Shapiro reaction,²⁹ the product of which was elaborated into dialdehyde 20. The formation of the B-ring was

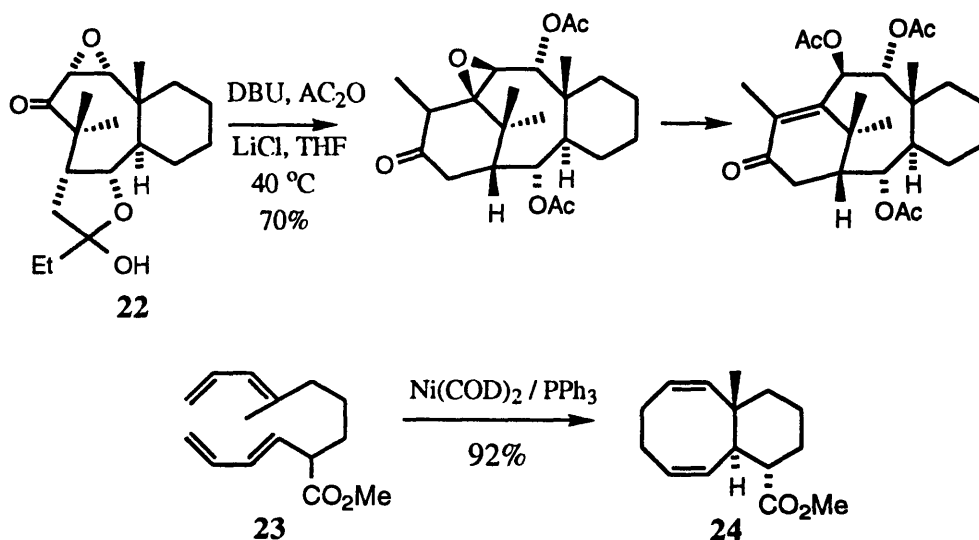
²⁹(a) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1. (b) Nicolaou, K. C.; Yang, Z.; Sorensen, E. J.; Nakada, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1024.

then accomplished from dialdehyde **20** through a McMurry coupling³⁰ to yield diol **21** in 23% yield.



Scheme 6: Nicolaou's AC->ABC strategy.

The final strategy is that of the BC->ABC order of ring formation. This strategy has been the subject of the least amount of research, as only two groups have published



Scheme 7: The BC->ABC carbocycle strategy.

³⁰McMurry, J. E. *Chem. Rev.* **1989**, 89, 1513.

work employing this strategy. Swindell uses this synthetic plan to develop a powerful tandem-aldol Payne rearrangement that not only creates the ABC tricyclic framework from the BC bicycle **22**, but it also sets the oxygen functionality of the C(9) and C(10) positions in taxusin.³¹ Wender also employs this plan in his tetraene cyclization of compound **23** to create the BC ring system **24**.³²

Many groups have employed, towards the synthesis of taxanes, a simplification of the eight-membered ring in the retrosynthetic direction by utilizing a connective transform³³ in conjunction with the above strategies. This transform connects two of the carbons of the eight-membered ring to form a bicyclic system that is structurally more complex than the eight-membered product (Scheme 8). This connection is an attractive transform for three reasons: (1) it allows for the construction of a six-membered ring -- a system that has been well-studied, and can be created through a variety of known reactions. (2) There are a large number of powerful reactions that can be utilized to create four-membered rings, the most powerful of which involves the [2+2] photocyclization of olefins, ketones, enones, or allenes. These reactions can, in many cases, be highly stereoselective. (3) The creation of a four-membered ring forms a highly strained system that can be readily fragmented to yield the desired eight-membered carbocycle.³⁴ This strategy is very efficient towards the synthesis of the taxane system, because it not only forms the difficult eight-membered ring, but it also provides carbonyl functionality that could be useful in the elaboration of the molecule.

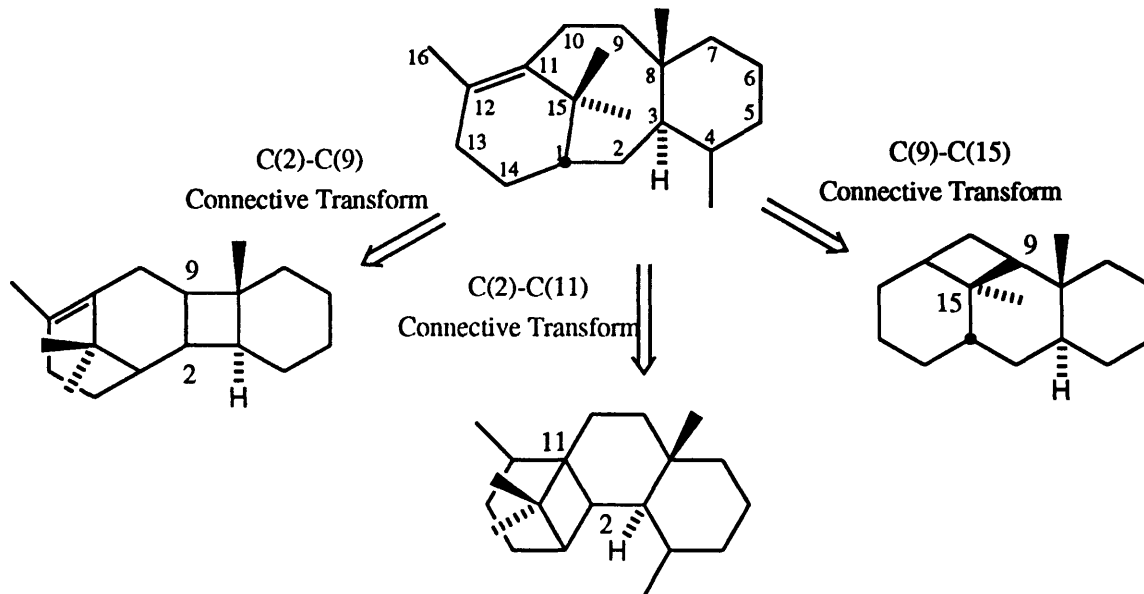
³¹Swindell, C. S.; Patel, B. P. J. *Org. Chem.* **1990**, *3*, 55.

³²Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221.

³³Corey, E. J.; Cheng, X. -M. *The Logic of Chemical Synthesis*, Wiley and Sons: New York, **1989**.

³⁴(a) de Mayo, P.; Takeshita, H.; Sattar, A. *Proc. Chem. Soc.* **1962**, 119. (b) Challand, B.; Hikino, H.; Kornis, G.; Lang, G.; de Mayo, P. *J. Org. Chem.* **1969**, *34*, 794.

Connective transforms have been utilized by a number of groups in their retrosynthetic planning of the synthesis of taxane systems. The three strategies that have been reported in the literature are shown in Scheme 8.



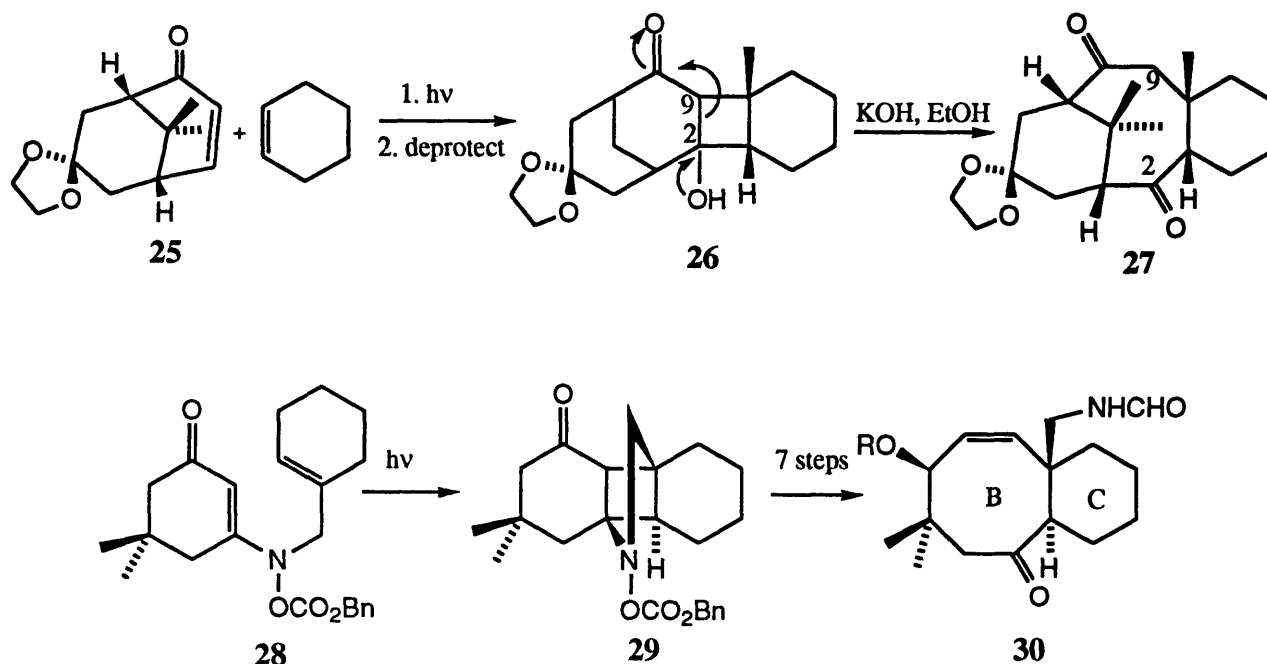
Scheme 8: Connective transforms of the carbocyclic skeleton.

The most popular of these connective transformations has been the C(2)-C(9) connective transform. This reconnection was utilized in synthetic efforts published by Blechert, where an intermolecular enone-olefin [2+2] photocyclization of **25** and cyclohexene was performed to afford fused carbocycle **26**.³⁵ This compound was fragmented with base to yield the taxane framework **27** consisting of the undesired *cis*-B-C ring fusion. This underscored the major problem faced by this connective transform strategy, as the [2+2] photocyclization yields, with few exceptions, the *cis* stereochemistry.

Swindell, however, found a way to overcome this shortcoming by performing an intramolecular enone-olefin [2+2] photocyclization of enone **28** which yielded the *trans*

³⁵Neh, H.; Kuhling, A.; Blechert, S. *Helv. Chim. Acta.* **1989**, 72, 101.

-fused compound **29**.³⁶ This compound was transformed in seven steps to the B-C bicycle **30** of the taxane framework.



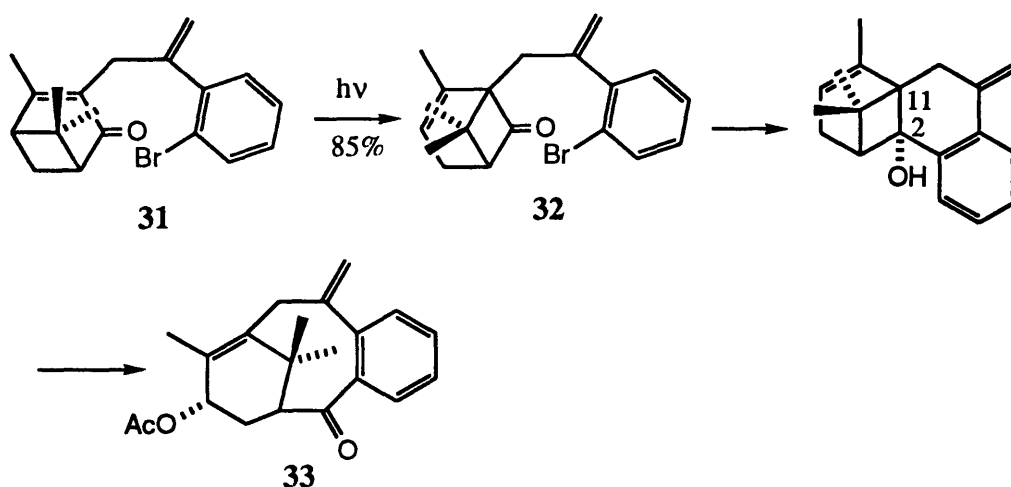
Scheme 9: Examples of C(2)-C(9) connective transform.

The second connective transform was utilized by Wender.³⁷ It connected the C(2) and the C(11) positions of the taxane framework. This strategy began with verbenone which was coupled to an aromatic side chain to yield compound **31**. Upon subjection to ultraviolet light, compound **30** underwent rearrangement to form compound **32**³⁸ which was transformed to the taxane tricyclic framework **33** in three steps.

³⁶Swindell, C. S.; Patel, B. P.; de Solms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346.

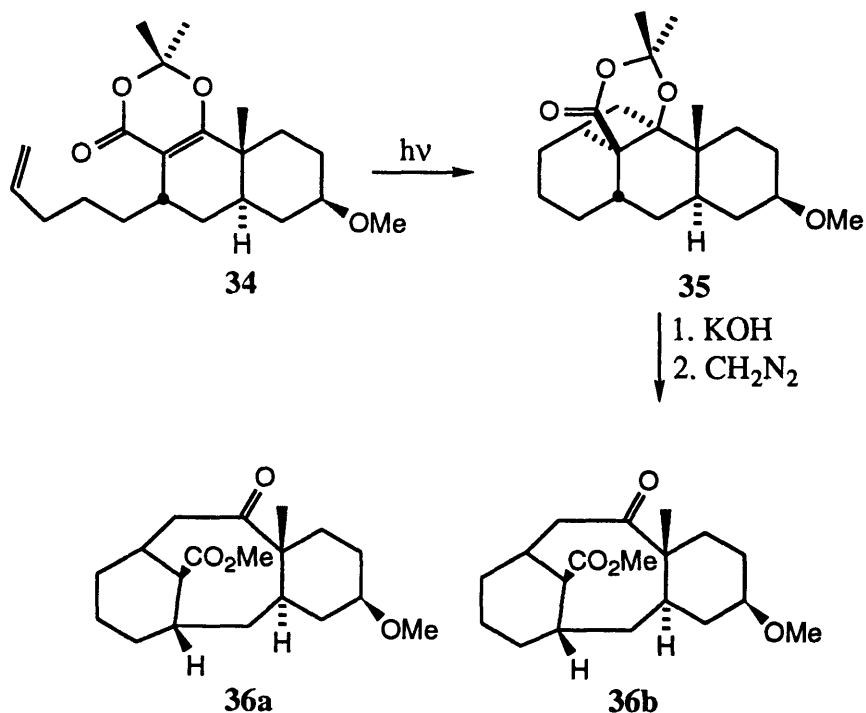
³⁷Wender, P. A.; Mucciario, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

³⁸Hurst, J. J.; Whitman, G. H. *J. Chem. Soc.* **1967**, *89*, 3828.



Scheme 10: Wender's C(2)-C(11) connective transformation.

The final connective transform that has been reported in the literature was performed by Winkler where a unique C(9)-C(15) was utilized (Scheme 11).³⁹ In this



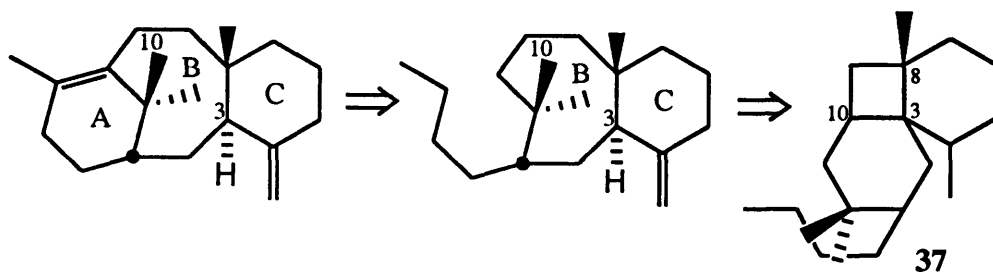
Scheme 11: Winkler's C(9)-C(15) connective transformation.

³⁹Winkler, J. D.; Lee, C. -S.; Rubo, L.; Muller, C. L.; Squattrito, P. J. *J. Org. Chem.* **1989**, *54*, 4491.

strategy, an intramolecular enone-olefin [2+2] photocyclization was performed on dioxenone **34** to afford photoproduct **35**, which underwent fragmentation with base to yield a mixture of tricycles **36a** and **36b**.

1.3 Retrosynthetic Analysis and Theory

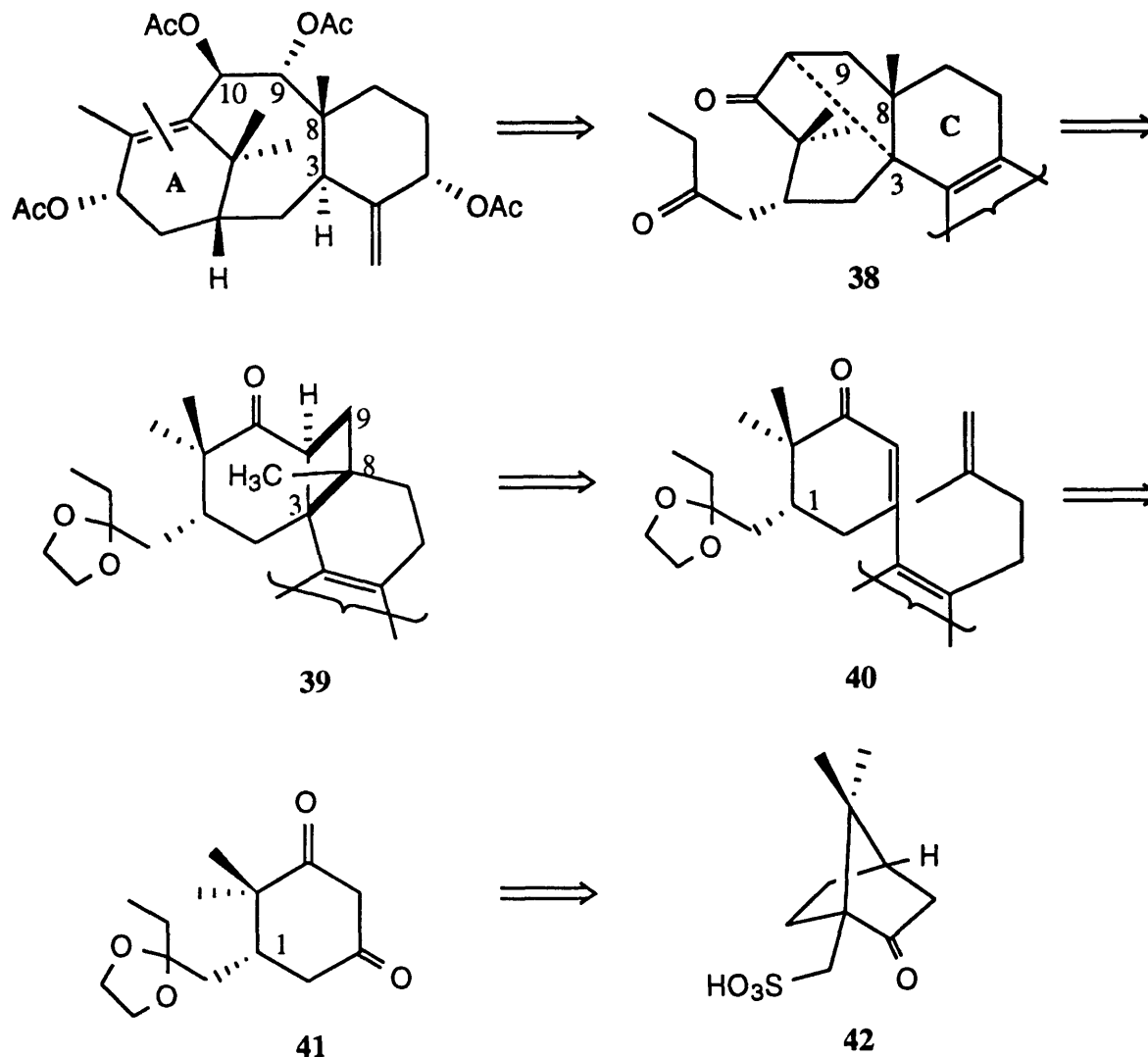
Our synthetic plan also possesses, as a key step, a connective transform; however, used in our synthesis is a novel, C(3)-C(10) connective transform (Scheme 12) that, through a [2+2] enone-olefin photocyclization, creates a unique tricyclo[4.0.1.0.4] dodecane carbocycle (compound **37**). This connective transform must first involve the disconnection of the A-ring, which, if intact in intermediate **37**, would involve extreme ring strain. Therefore, this synthetic plan follows the BC->ABC order of ring formation. This transformation is an attractive strategy because it would establish the stereochemistry of the C(8) methyl group, while allowing the stereochemistry at the C(3) ring juncture to be established in a subsequent step.



Scheme 12: Proposed taxane carbocycle C(3)-C(10) connective transform.

The general retrosynthetic analysis for the aforementioned plan is outlined in Scheme 13. The first disconnection is that of the A ring. In the forward direction this ring should be constructed through an aldol closure and dehydration of diketone **38** to form the enone. The next major disconnection is the transform of the C(3) - C(10) connection to give intermediate **39**. This cyclobutane intermediate **39** should be derived from a [2+2] enone - olefin photocyclization of cyclohexenone **40**, the desired stereochemistry of which would be the result of the approach of the olefin to the enone face opposite that of the side

chain at the C(1) position. The photosubstrate **40** should be the product of a coupling reaction between a side chain adduct and a derivative of the key intermediate diketone **41**.



Scheme 13 : General retrosynthetic plan.

This diketone is an important intermediate, because it not only possesses the desired stereochemistry at the C(1) position of the molecule which is necessary to direct the stereochemical outcome of the key photocyclization step, but it also could serve as a

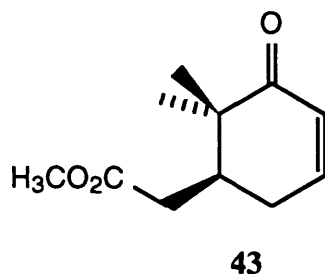
strategic precursor to a variety of photosubstrates for the synthesis of taxane analogs. Diketone **41** should be derived from the chiral pool molecule, (1*S*)-(+)-10-camphorsulfonic acid (**42**).

The desired functionality of the C ring was not known during the planning stages of this project. Functional groups that could be easily transformed into the functionality found in taxusin were desirable; however, it was imperative to include groups that would lead to the correct stereochemical outcome of the key [2+2] photocyclization step.

Chapter 2. Previous Work

Initial work on this project was performed in our laboratories by Mr. Edward Licitra. His work dealt with two major issues: 1) the efficient, enantioselective synthesis of the key diketone intermediate **41**, and 2) the incorporation of an olefin functional group onto the side chain of the photosubstrate **40**, and a subsequent attempt of the [2+2] photocyclization.

The synthetic plan for the construction of diketone **41** closely followed that of a similar molecule **43** prepared by Liu in a synthesis of khusimone.⁴⁰ Slight modifications of the synthetic strategy for Liu's intermediate **43** afforded the desired ketone in 7 steps and 29% yield from readily available (1*S*)-(+)-10-camphorsulfonic acid (See Scheme 14).



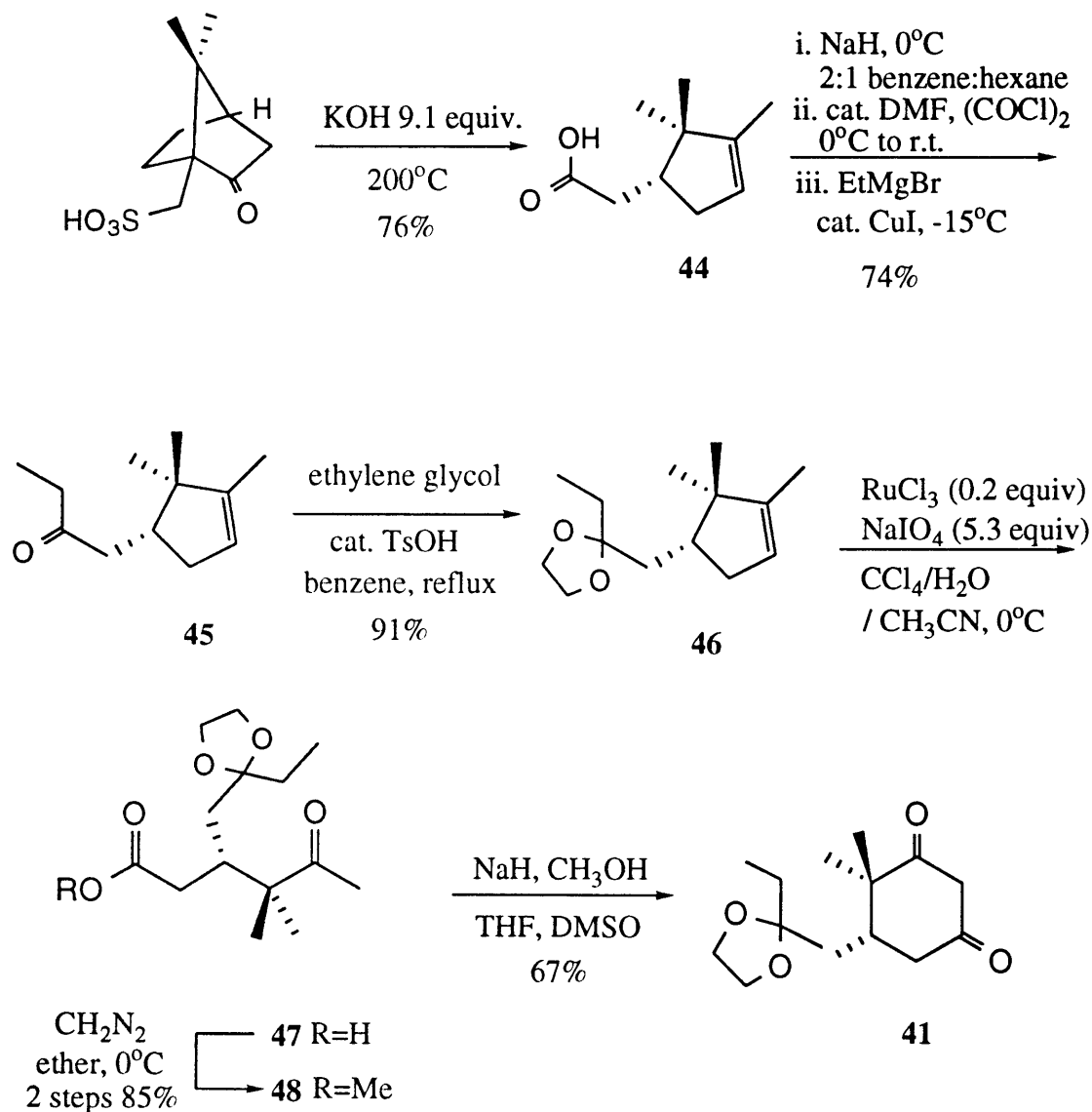
Synthesis of intermediate diketone **41** began with (1*S*)-(+)-10-camphorsulfonic acid which was converted to campholenic acid **44** through an alkali fusion reaction⁴¹ in 76% yield. In recent work by Ms. Rebecca Carazza, the ethyl ketone **45** was made in a one pot conversion, from campholenic acid through transformation of the carboxylic acid to the acid chloride with sodium hydride and oxalyl chloride; then, after removal of the excess oxalyl chloride *in vacuo*, the acid chloride was converted directly to ethyl ketone **45** with ethylmagnesium bromide and catalytic cuprous iodide⁴² in 74% yield overall. The ethyl

⁴⁰ Liu, H. - J.; Chan, W. H. *Can. J. Chem.* **1979**, *57*, 708.

⁴¹ Crist, B. V.; Rodgers, S. L.; Lighter, D. A. *J. Am. Chem. Soc.* **1982**, *104*, 6040.

⁴² Fujisawa, T.; Sato, T. *Org. Synthesis*. **1987**, *66*, 116.

ketone was then protected as the ethylene ketal by heating it at reflux with a catalytic amount of *p* - toluenesulfonic acid and excess ethylene glycol in benzene, and the olefinic bond was then oxidized with catalytic ruthenium tetroxide to afford keto-acid **47**. This reaction was performed using a solvent mixture of acetonitrile, carbon tetrachloride, and



Scheme 14: Synthesis of diketone **41** from camphorsulfonic acid.

water that was developed by Sharpless⁴³, as opposed to the usual mixture of only carbon tetrachloride and water. In the Sharpless system, it was postulated that the acetonitrile acts as a ligand for the low valent ruthenium produced during the reaction. In the absence of acetonitrile, the carboxylic acids formed during the reaction create insoluble material that removes the catalyst from the catalytic cycle.

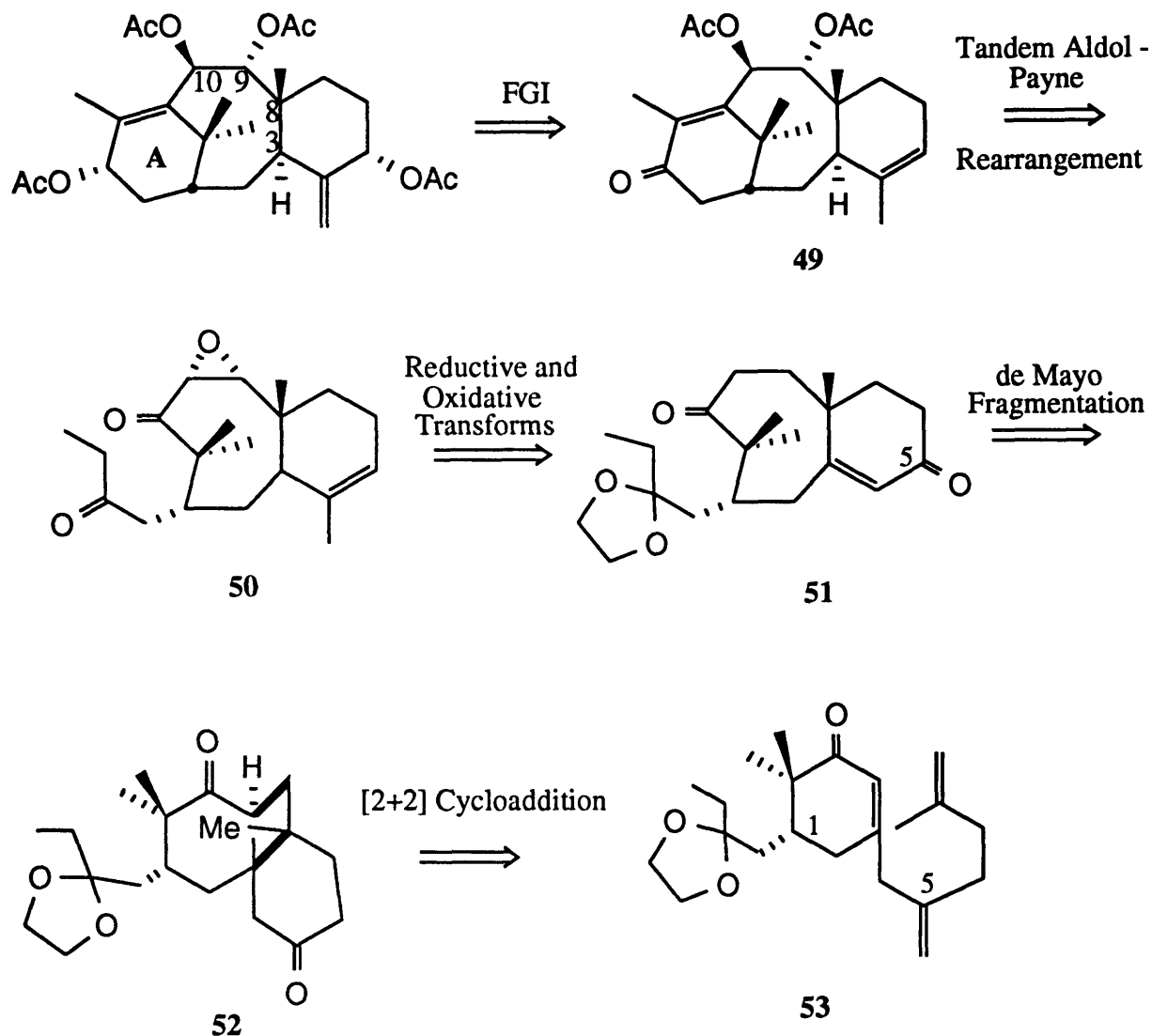
The synthesis of diketone **41** was completed by the conversion of carboxylic acid **47** to the corresponding methyl ester with diazomethane, followed by a Dieckmann cyclization of the methyl ester **48** with sodium methoxide. Diketone **41** was recrystallized from ether and tetrahydrofuran to afford the key intermediate in 60% yield from ethylene ketal **46**.

Following the successful synthesis of the diketone **41**, the next challenge was to design and synthesize a photosubstrate that would be useful towards the synthesis of the target molecule. It was decided that a simple olefin functional group appended to the photosubstrate side chain would be an attractive target (see Scheme 15). This molecule (compound **53**) was deemed appropriate for the following reasons: 1) it could be easily converted through oxygenation with ozone to a compound that would aid in the fragmentation of the cyclobutane ring; 2) the resulting enone could be readily converted, through functional group interconversions, to the functionality found on the C ring in the target molecule; 3) the olefin group was small enough not to sterically hinder the stereochemical outcome of the photocyclization; and 4) the olefin, at the C(5) position, was strategically placed $\delta - \epsilon$ to the carbonyl of the enone so it would not participate electronically with the excited enone, and thus effect the outcome of the photocyclization.

Consequently, the specific synthetic plan that was first envisioned for the project is shown in Scheme 15. The first conversion involved the C-ring functionality. In the retrosynthetic direction, the C(5) acetate group was removed and replaced with an internal double bond (compound **49**). The allylic acetate functionality was envisioned to be the

⁴³ Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

result, in the forward direction, of an epoxidation of the internal olefinic bond in compound **49**, followed by fragmentation with base. The next major disconnection was that of the A ring. This ring closure was expected to be accomplished through a tandem aldol-Payne



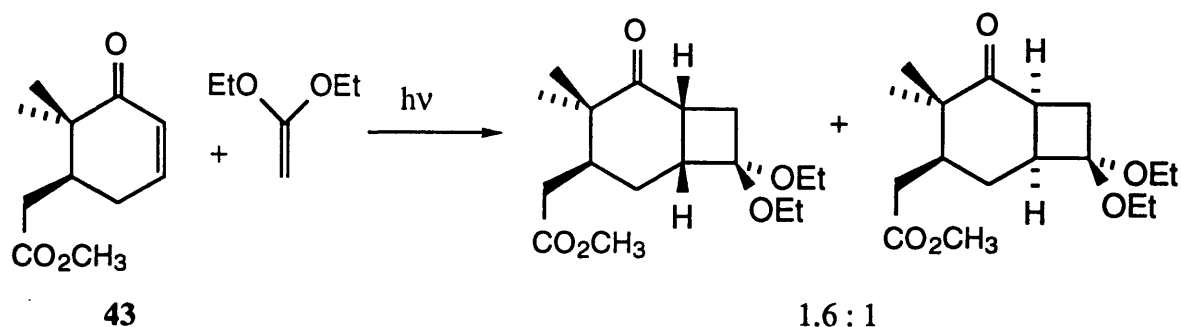
Scheme 15 : Synthetic plan for the construction of taxusin.

rearrangement of epoxy diketone **50**. This reaction was performed by Swindell on a compound similar to epoxy ketone **50** in his studies towards the synthesis of taxanes.⁴⁴ The tandem aldol-Payne rearrangement was expected to be a very powerful reaction for

⁴⁴ Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3.

taxane synthesis, because it not only would result in the cyclization of the A ring, but it would also set the stereochemistry of the C(9) and C(10) acetate groups. Oxidative and reductive transformations would effect the conversion of enone **51** to epoxy diketone **50**. Enone **51** would be the direct product of a retro-Michael fragmentation of the oxidized photoproduct **52**, the C(5) olefin of which would be the result of an enone-olefin [2+2] photocyclization of photosubstrate **53**.

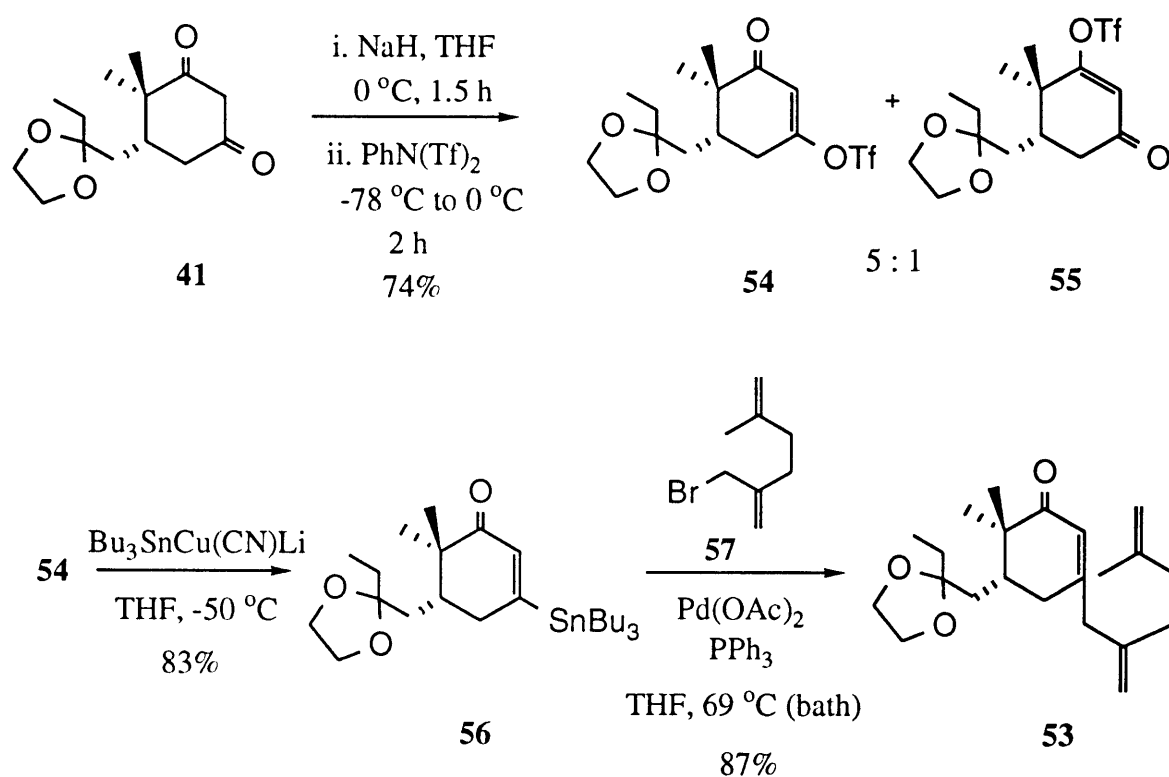
It was expected that the stereochemical outcome of the [2+2] photocyclization would be the result of the approach of the olefin to the enone face opposite that of the C(1) side chain. This facial selectivity was necessary for the generation of the correct C(8) stereochemistry in taxusin. Relatively few studies had been performed on diastereoselective photocyclizations of systems where the only chiral center present in the molecule was two carbons removed from the enone double bond reactive site; however, Liu had conducted studies on intermolecular cycloadditions, focusing on a molecule similar to enone **53**. These studies (see Scheme 16) revealed that a molecule with only one chiral center removed from the reactive center could afford a certain degree of facial selectivity. His studies focused on the intermolecular enone-olefin [2+2] photocyclization of compound **43** and 1,1-dimethoxyethene.⁴⁰ Experimental results determined that the ratio



Scheme 16

of product isomers were 1.6:1 favoring attack on the face opposite of that of the side chain. Through extension of this precedent to our intramolecular system, it was concluded that the favored product of the photocyclization of compound **53** would possess the desired stereochemistry.

Consequently, the synthesis of photosubstrate **53** was accomplished through a convergent route which allowed for the coupling of side chain **57** (see Scheme 17) with vinyl stannane **56**, a derivative of diketone **41**. Side chain **57** was prepared in 5 steps from 3-methyl-3-butene-1-ol.⁴⁵ Vinyl stannane **56** was synthesized in two steps from

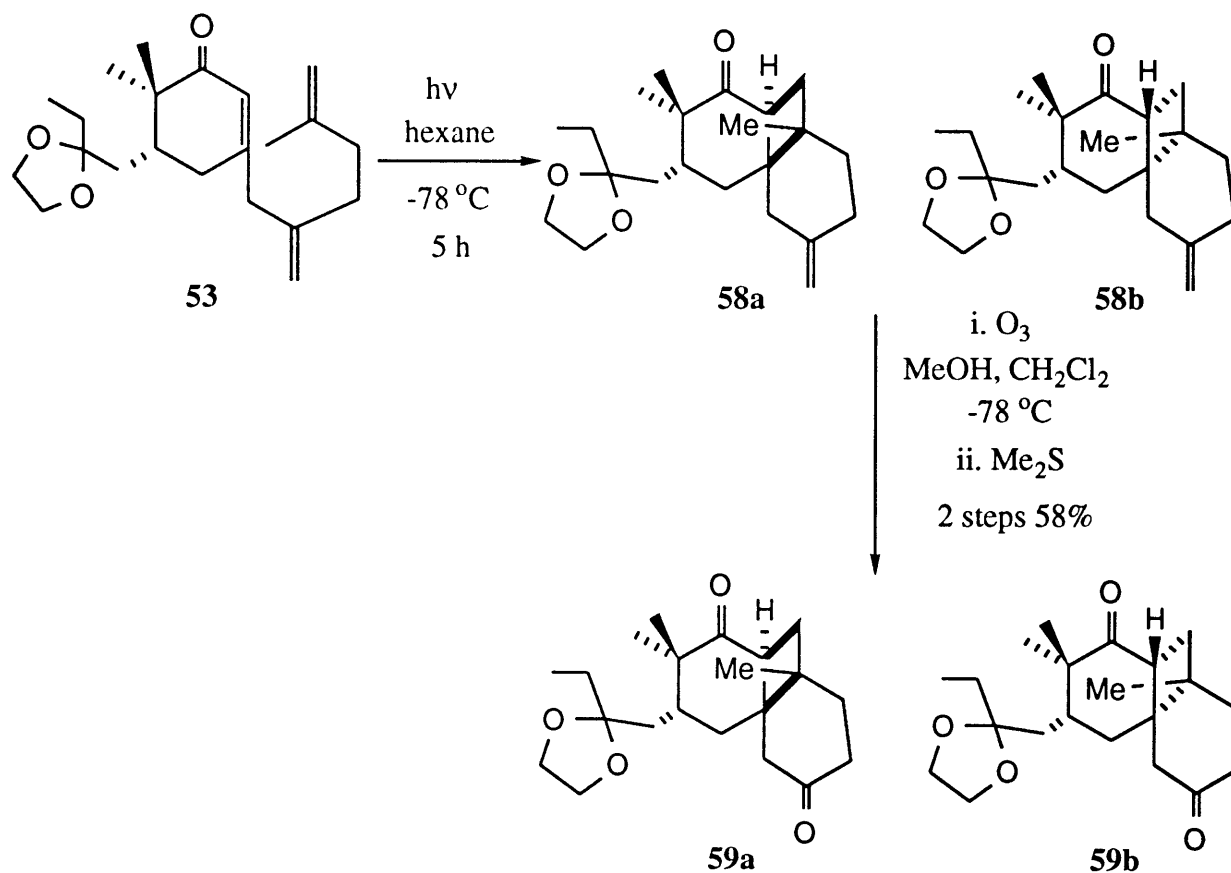


Scheme 17 : Synthesis of photosubstrate.

diketone **41**. First, enol triflate **54** was prepared with sodium hydride and *N*-phenyltrifluoromethanesulfonimide to give a 5:1 ratio of regioisomers **54:55**. *N*-

⁴⁵ Marshall, J. A.; Anderson, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, 32, 113.

phenyltrifluoromethanesulfonimide was used for its sensitivity to steric factors, since previous synthetic attempts with trifluoromethanesulfonic anhydride afforded only a 1:1 mixture of the two enol triflates. Vinyl stannane **56** was prepared from enol triflate **54** through a 1,4 addition of tributyltin cyanocuprate⁴⁶ which caused the elimination of the triflate leaving group. Synthesis of the photosubstrate was completed through a palladium(0) coupling of vinyl stannane **56** and allylic bromide **57** with palladium(II) acetate and triphenylphosphine.



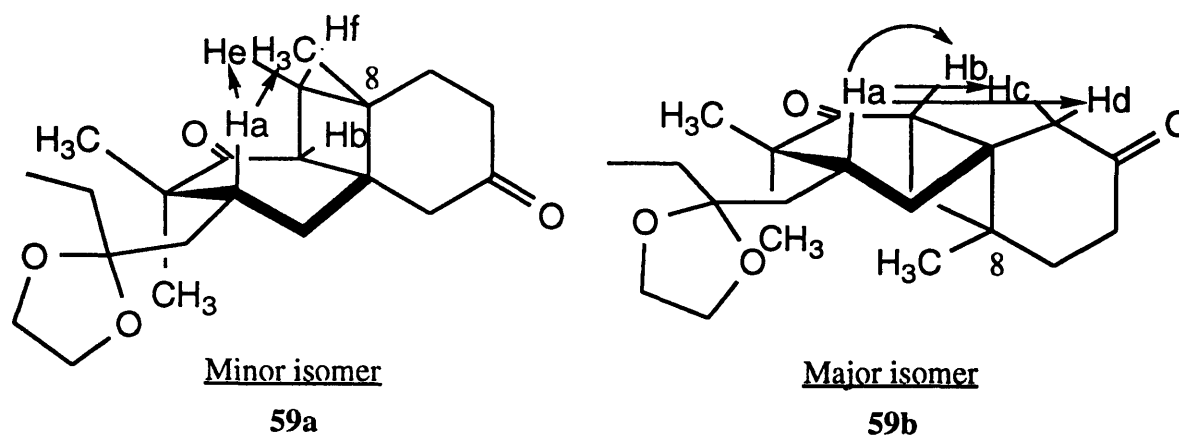
Scheme 18

Photosubstrate **53** was then photocyclized under a variety of conditions to determine the optimum solvent and temperature that would afford the best ratio of major: minor isomers. Cyclization in a mixture of dichloromethane and hexane at $-78\text{ }^{\circ}\text{C}$

⁴⁶ Seitz, D. E.; Lee, S. -H. *Tetrahedron Lett.* **1981**, 22, 4909.

produced a 7:1 ratio of major:minor isomers, while reaction in hexane resulted in only a 1.5:1 ratio. Separation of the resulting mixture of isomers proved difficult; consequently, the product was oxidized with ozone at $-78\text{ }^{\circ}\text{C}$ to afford the corresponding ketone mixture which could be separated by flash column chromatography (compounds **59a** and **59b**). (see Scheme 18).

Determination of the stereochemistry of the major and minor isomers was performed through nOe difference studies on the ketone isomers **59a** and **59b** along with the major isomer from the photocyclization. The results of these experiments (Scheme 19) showed definitively that the major isomer of the photocyclization was the undesired isomer (photoproduct **58b**), the product resulting from the approach of the side chain to the same side of the ketal side chain. The nOe difference experiments of the major isomer (photoproduct **59b**) showed a three percent nOe from the irradiated H_a to the cyclobutane proton H_b , and a four percent nOe to the protons α to the ketone H_c and H_d . Irradiation of



Scheme 19 : Analysis of ^1H - ^1H nOe difference spectra of oxidized photoproduct.

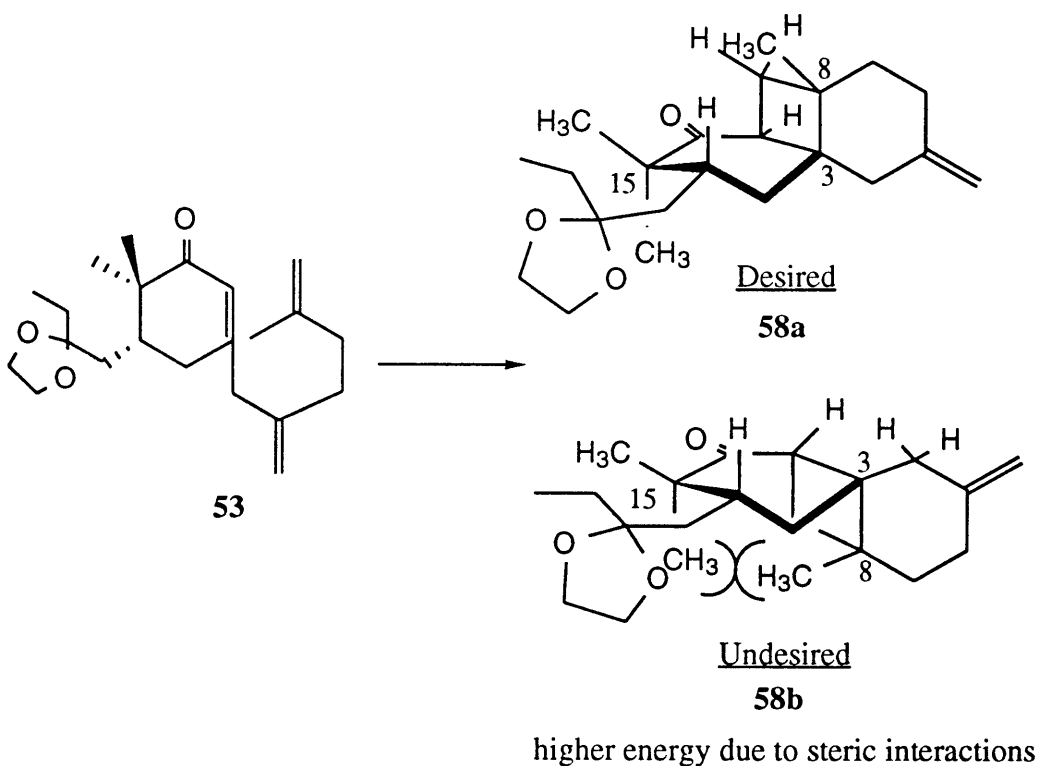
H_a in the minor isomer (**59a**) showed a two percent nOe to H_e on the cyclobutane ring and a four percent nOe to the cyclobutane methyl group. H_e and H_b were easily differentiated in the ^1H NMR spectrum, because H_e had a large geminal coupling constant to H_f , while H_b showed coupling to no geminal partner.

From these nOe difference studies, it was determined that the undesired : desired (**58b:58a**) product ratio was, at worst, 7:1 using a solvent mixture of dichloromethane and hexane at -78 °C, and, at best, using only hexane at 40 °C, 1.5:1. Additional reactions were conducted at elevated temperatures and using various solvent mixtures in hopes of reversing the stereochemical outcome of the reaction, but with no avail; consequently, it was determined that the photocyclization of photosubstrate **53**, using the C(5) olefin functionality would not be practical or useful in the synthesis of taxusin.

Chapter 3. Synthesis of the *trans*-BC Ring System

3.1 Analysis of the Previously Attempted Photocyclization

Without the ability to create a reversal in the stereochemical outcome of the photocyclization of olefin photosubstrate **53**, the present author inherited the project which, in order to be successful, faced two options (1) a discovery of some functionality with which to replace the olefinic double bond that would cause the photocyclization to favor the opposite facial selectivity, or (2) a replanning of the entire synthetic route. Efforts to locate literature examples where the stereochemical outcome of [2+2] enone-olefin photocyclizations were reversed by either varying inherent functionality or varying reaction



Scheme 20: Comparison of energetics of the two product isomers afforded in the photocyclization.

conditions proved to be futile. Cases could be found where product ratios were changed using varied reaction conditions, but a total reversal of stereochemistry could not be found.

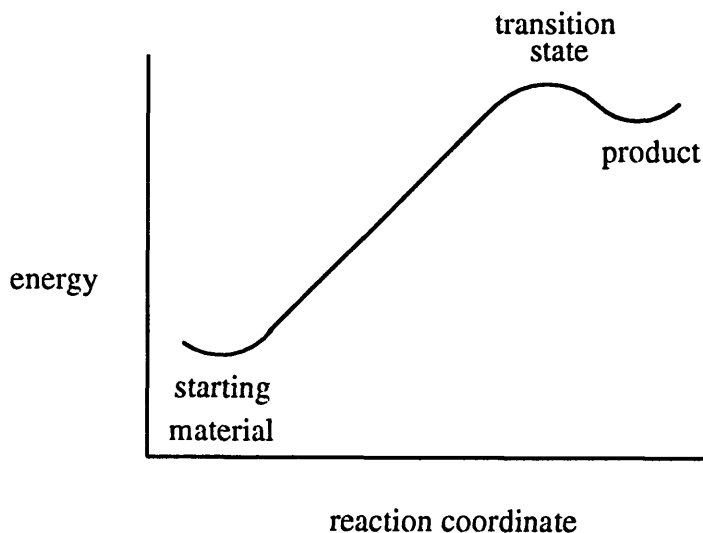
An analysis of the hypothesis that was applied to predict the stereochemical outcome of the previously attempted photocyclization was necessary in order to gain insight into the failure of the reaction and to envision new strategies that could result in the desired stereochemistry (Scheme 20). The original strategy was based on the expectation that the undesired isomer (**58b**) would be highly disfavored due to severe steric interactions between the C(8) methyl and the C(15 α) geminal methyl, whereas the desired product isomer (**58a**) was assumed to possess no such steric interactions. Furthermore, it was believed that the approach of the double bond would favor the enone face opposite the bulky ketal C(1) side chain. Since it had been discovered that isomer **58b** was, in fact, the favored product under all conditions attempted, a more in depth study of the reaction dynamics was undertaken.

An initial molecular mechanics calculation using the CHARMM program⁴⁷ supported our expectation that isomer **58b** was the higher energy isomer. The calculations were performed by first constructing both isomers into the program and allowing the system to minimize the energy of each conformation. Minimization of the conformation energies was simple due to the fact that the cyclobutane moiety contained only one degree of freedom. From the calculations it was determined that the undesired isomer (**58b**) was 7 kcal/mol higher in energy than the desired isomer (**58a**). The calculations were then repeated excluding the energy minimizations. This was done with the assumption that during the reaction, the enone plane and the reactive olefin plane would possess no degrees of freedom due to the requirement that the reactive olefin be in perfect alignment with the excited enone during the cyclobutane formation (evident in Scheme 22, intermediates **60a**

⁴⁷ Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comp. Chem.* **1983**, *4*, 187.

and **60b**). These calculations revealed that the structure of the undesired isomer (**58b**) was 15 kcal/mol higher in energy than that of the desired isomer (**58a**).

The results of these calculations suggests that the stereochemical outcome is being determined by factors other than energy differences in the products. An assumption that states that the differences in energy levels of the products would be the determining factor of the stereochemical outcome of the reaction is an application of the Hammond Postulate.⁴⁸ According to this theory, if the product is of higher energy than that of the starting material then the transition state of the reaction is proposed to resemble the products (known as a late stage transition state). This is because, since the starting material is of lower energy, considerable reorganization is required to reach the transition state (Scheme 21). In a rigorous sense, however, the Hammond Postulate is not applicable to a photochemical reaction, because it oversimplifies the mechanism, which is complex and consists of multiple intermediates.



Scheme 21: Graphical representation of the Hammond Postulate.

⁴⁸ Hammond, G. S. *J. Am Chem. Soc.* **1955**, *77*, 334.

A more thorough analysis of the photocyclization mechanism suggests that the question of stereochemistry is more complex than was first assumed. A review of enone-olefin photocyclization reactions by Crimmins has compiled most of the mechanistic results relevant to synthetic organic chemistry.⁴⁹ Absorption of a photon by the ground state enone initially produces an excited singlet $E^*{}^1$ (either $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$)⁵⁰ which can (1) combine with the ground state singlet to form a singlet exciplex $[E^* \cdots A^0]^1$, (2) undergo intersystem crossing to form an excited triplet $E^*{}^3$, or (3) undergo relaxation back to the ground state (known as reversion). The most common pathway for the singlet to progress in an enone excitation is intersystem crossing and conversion to the triplet excited state, since intersystem crossing, particularly in five- and six-membered enones, is an efficient process. The excited triplet can then either decay back to ground state or combine with the ground state alkene to form a carbon-carbon bond and produce a triplet 1-4 diradical which must undergo spin inversion to the singlet diradical before formation of the second carbon-carbon bond can occur.⁵¹ Additionally, at any point in the reaction sequence until the formation of the intact cyclobutane, reversion can occur resulting in the recreation of the ground state of both the enone and the olefin.

In photocyclization reactions where a stereogenic center is present in the excited state enone which exists as a cyclohexenone, a useful rationale has been used to analyze the stereochemical course of the reaction. This rationale states that the ground state alkene will attack the most stable conformation of the excited state enone in which the β carbon is substantially pyramidalized.⁵² A previous example supporting this theory is the addition of allene to 3,4-dimethylcyclohexenone⁵³ (Fig.1). Here, the most stable conformation of the

⁴⁹ Crimmins, M. T.; Reinhold, T. L.; *Organic Reactions* **1993**, 77, 297.

⁵⁰ (a) Turro, N. J. *Modern Molecular Photochemistry*; Benjamin Cummings; Menlo Park, CA, **1978**, p. 458. (b) Schuster, D. I.; Bonneau, R.; Dunn, D. A.; Rao, J. M.; Jossot-Dubieu, J. *J. Am. Chem. Soc.* **1984**, 106, 2706. (c) Chan, C. B.; Shuster, D. I. *J. Am. Chem. Soc.* **1982**, 104, 2928.

⁵¹ (a) Stephenson, L. M.; Brauman, J. I. *J. Am. Chem. Soc.* **1971**, 93, 1988. (b) Loufty, R. O.; DeMayo, P. *Can. J. Chem.* **1972**, 80, 3465.

⁵² (a) Wiesner, K. *Tetrahedron* **1975**, 3, 1655. (b) Marini Bettolo, G.; Sahoo, S. P.; Poulton, G. A.; Tsai, T.; Wiesner, K. *Tetrahedron* **1980**, 36, 719. (c) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1960**, 82, 1512.

⁵³ Ziegler, F. E.; Reid, G. R.; Studt, W. C.; Wender, P. A. *J. Org. Chem.* **1977**, 42, 1991.

excited state triplet is the chair-like conformation where both methyl groups exist in an equatorial position; consequently, at -78 °C the addition of allene results in the axial approach *cis* to the C(4) methyl group.

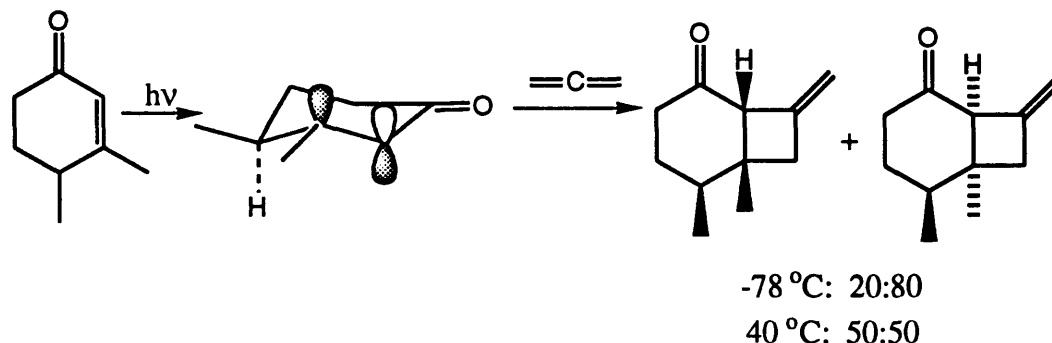


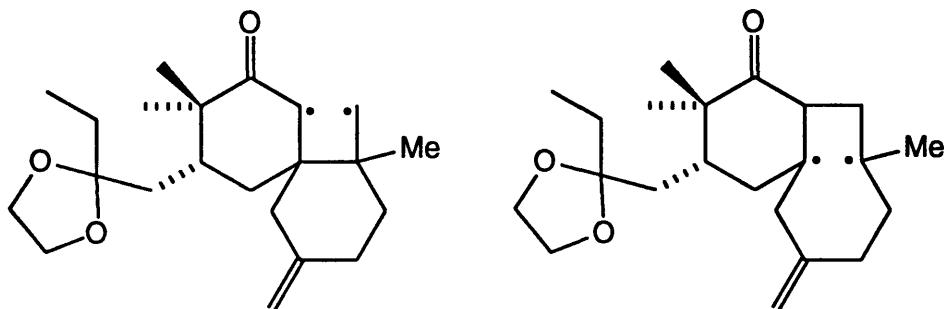
Figure 1: Analysis of the addition of allene to 3,4-dimethylcyclohexenone.

An understanding of the order of bond formation is essential in predicting the stereochemical outcome of the reaction. In simple alkene systems that do not incorporate electron donating atoms attached to either the enone or reacting alkene, it can be expected that the carbon-carbon bond α to the ketone will be the first to form. This is because the charge distribution of the excited enone is the opposite of its ground state configuration, and thus the enone β -carbon bears a partial negative charge while the enone α -carbon bears a partial positive charge.⁵⁴ Therefore, the olefin π system interacts with the partial positive charge of α -carbon of the excited enone triplet to first form the carbon-carbon bond α to the carbonyl.

The order of bond formation can also be predicted by comparing the possible 1,4-diradicals that are the result of the formation of the first carbon-carbon bond (Scheme 22). Usually, the more stable 1,4-diradical system will predominate. In the case of the cyclization of photosubstrate **53**, formation of the bond β to the carbonyl, as the first

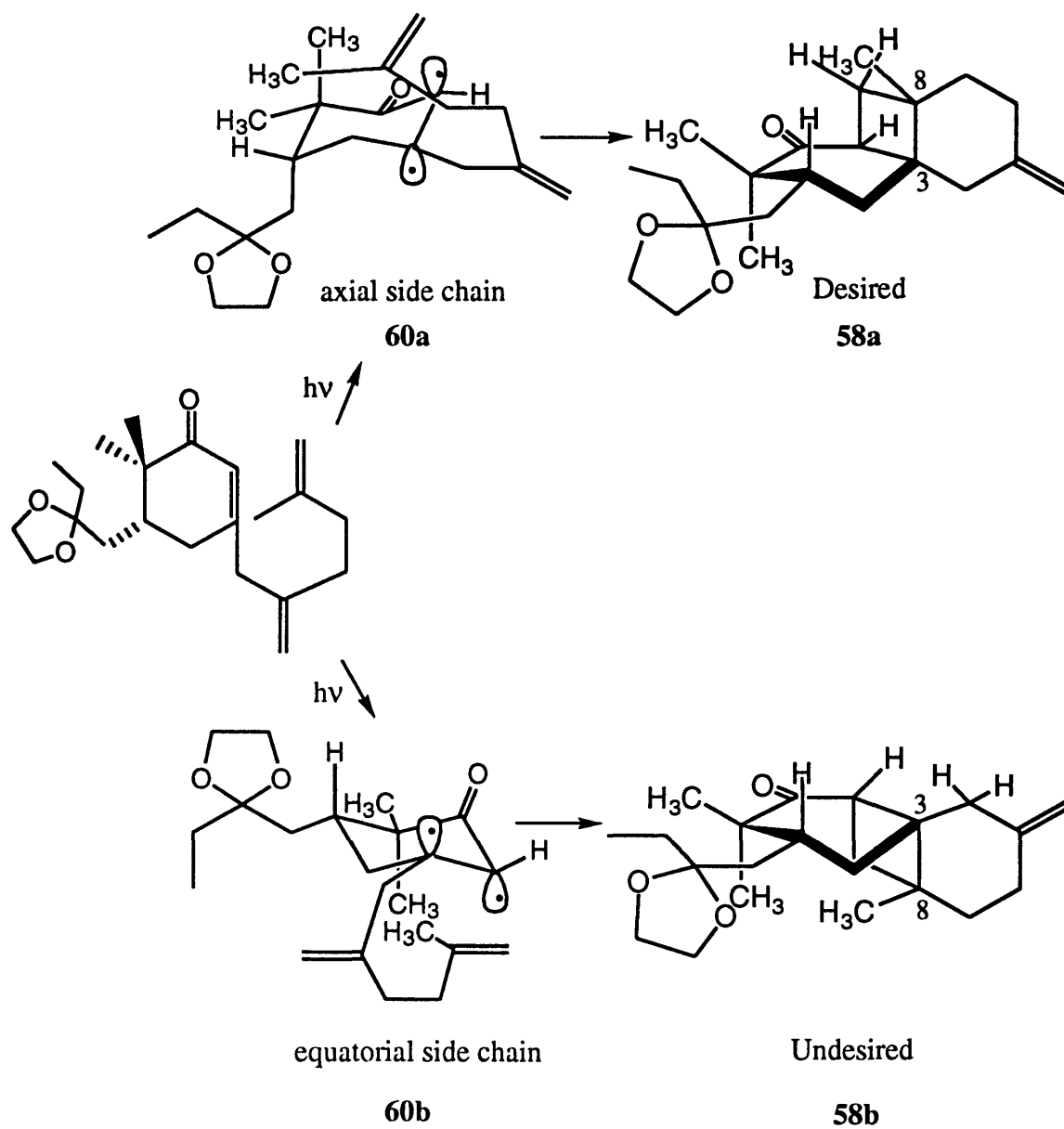
⁵⁴ Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570. (b) Burnstein, K. Y.; Serebryakov, E. P. *Tetrahedron* **1978**, *34*, 3233. (c) Zimmermen, H. E.; Binkley, R. W.; McCullough, J. J.; Zimmerman, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 6589.

carbon-carbon bond, will result in the formation of a secondary radical and a primary radical, whereas the formation of the bond α to the carbonyl, as the first bond, results in two tertiary radicals. Therefore, the bond α to the carbonyl group will be the first to form.



Scheme 22: Comparison of the possible 1,4-diradicals resulting from the formation of the first carbon-carbon bond in the photocyclization.

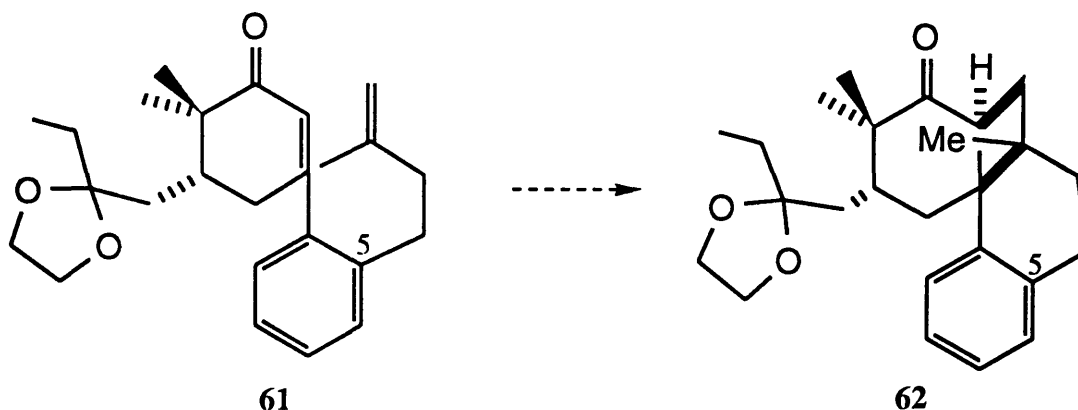
Using the aforementioned β -pyramidalization theory, an examination of the triplet enone excited state in our reaction shows that it can exist in two different conformations (Scheme 23). In **60b**, the large ketal side chain is in an equatorial position on the cyclohexane ring, while in **60a** the side chain is axial. Intermediate **60b** results in the formation of the major, undesired isomer **58b**, while intermediate **60a** affords the minor, desired isomer **58a**. Following the same reasoning for the stereochemical outcome of the attack of allene on 3,4-dimethylcyclohexenone, it can be assumed that intermediate **60b** is the lower energy conformation of the excited state triplet due to the more stable equatorial positioning of the C(1) ketal side chain; therefore, it can be expected that the major isomer of the reaction would be **58b**.



Scheme 23: Comparison of triplet excited state conformations leading to isomers **58a** and **58b**.

3.2 Model System Studies

With a better understanding of the factors determining the stereochemical outcome of the photocyclization, it was necessary to design a new system. It seemed plausible that since the two factors which were affecting the stereochemical outcome of the reaction were conformation and energetics, finding a way to alter one or both of these factors could result in a change in the outcome of the reaction. Consequently, a system was designed that not only could place conformational restrictions on the excited state, but could also result in a lowering of the excited state free energy. The designed system (Scheme 24) was one where the olefin functionality at the C(5) position was replaced with an aromatic ring

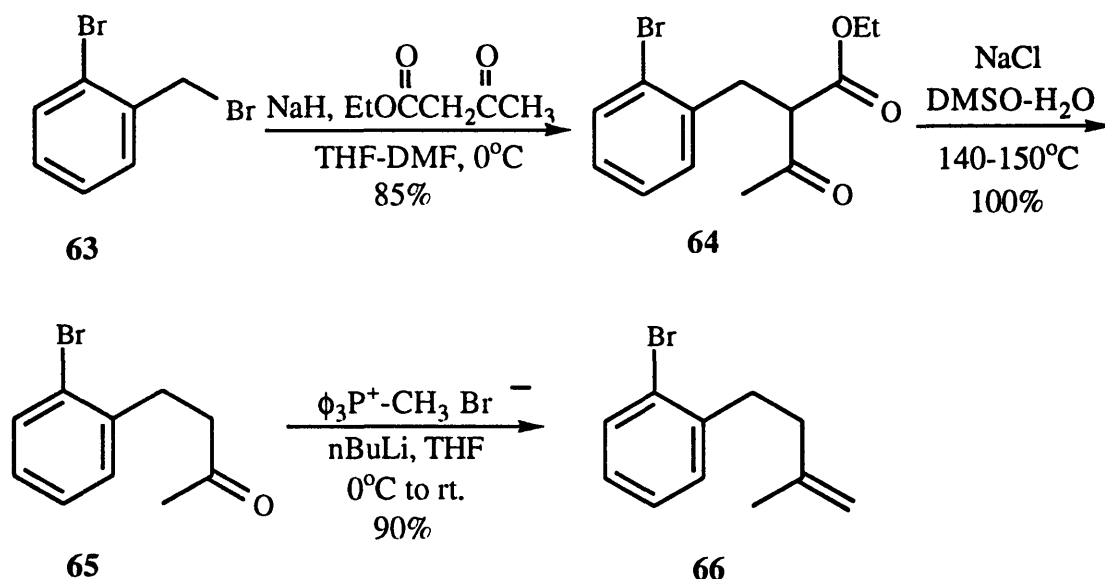


Scheme 24: Proposed route to affect a reversal of stereochemistry.

(compound **61**). This system was thought to be an improvement over the previous one, because (1) conjugation of the aromatic ring with the enone system would result in a lowering of excited state energetics, (2) the aromatic ring would cause the system to be conformationally more rigid due to the necessity of the aromatic π -system to be coplanar with the benzylic radical of the excited state, and 3) an aromatic ring could not participate in

reactions such as *cis* - *trans* isomerization⁵⁵ that are known to compete with intersystem crossing in acyclic systems that are not rigidly held.⁵⁶

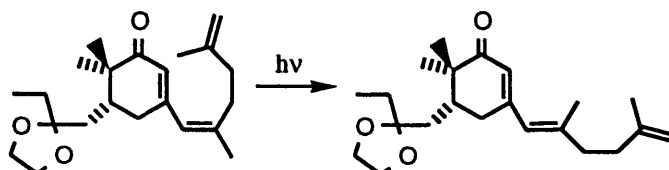
Synthesis of the aromatic side chain **66** was achieved in three steps from 2-bromobenzyl bromide (**63**) in 77% yield (Scheme 25). The sequence began with the alkylation of 2-bromobenzyl bromide (**63**) with the sodium anion of ethyl acetoacetate at 0 °C. The resulting β -keto ester **64** was dealkoxycarbonylated in quantitative yield using Krapcho conditions,⁵⁷ *i.e.* sodium chloride, dimethyl sulfoxide, and water, then the olefin functionality was formed from ketone **65** with methyltriphenylphosphonium bromide and *n*



Scheme 25: Synthesis of aromatic side chain.

⁵⁵ DeMayo, P.; Nicholson, A. A.; Tchir, M. F. *Can. J. Chem.* **1969**, *47*, 711.

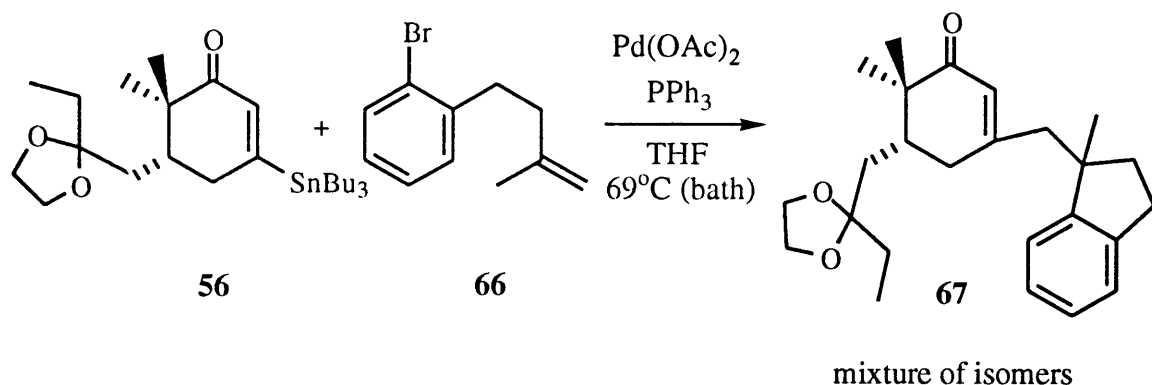
⁵⁶ In previous work by Mr. Ed Licitra, a side chain with a simple C(4)-C(5) olefin was employed. Photocyclization resulted only in *cis-trans* isomerization. Licitra, E. J. Research Report, Massachusetts Institute of Technology, 1993.



⁵⁷ (a) Borowiecki, L.; Kazwoski, A. *Pol. J. Chem.* **1978**, *52*, 1447. (b) for a review of dealkoxycarbonylation see: Krapcho, P. *Synthesis* **1982**, 893.

-butyllithium.⁵⁸ Although this side chain lacked the functionality necessary to effect a useful cleavage of the aromatic ring to be elaborated into a functionalized taxusin C-ring, it would serve as a model compound to test the viability of the photochemical [2+2] cyclization and subsequent fragmentation.

With large amounts of the aryl bromide side chain in hand, the next step was to find a method to affect the coupling of a derivative of diketone **41** to side chain **66**. The first method that was attempted was the zero valent palladium coupling reaction⁵⁹ that was used in the previous route. A mixture of vinyl stannane **56** (Scheme 26), aryl side chain **66**, palladium(II) acetate, and triphenylphosphine were heated in tetrahydrofuran to yield a coupled product; however, the product proved to be tricyclic compound **67**. Apparently, before the intermolecular coupling had occurred, an intramolecular Heck reaction transpired between the aryl-palladium bromide intermediate and the pendant olefin.⁶⁰ Transmetalation and coupling to the enone presumably occurred in a later step. Attempted coupling of the corresponding aryl stannane and enol triflate **54**⁶¹ resulted in an identical tricyclic product.



Scheme 26: Attempted Stille coupling.

⁵⁸ (a) Wittig, G.; Geissler, G. *Leibigs Ann Chem* **1953**, *44*, 580. (b) Wittig, G.; Schollkopf, U. *Chem Ber* **1954**, *87*, 1318.

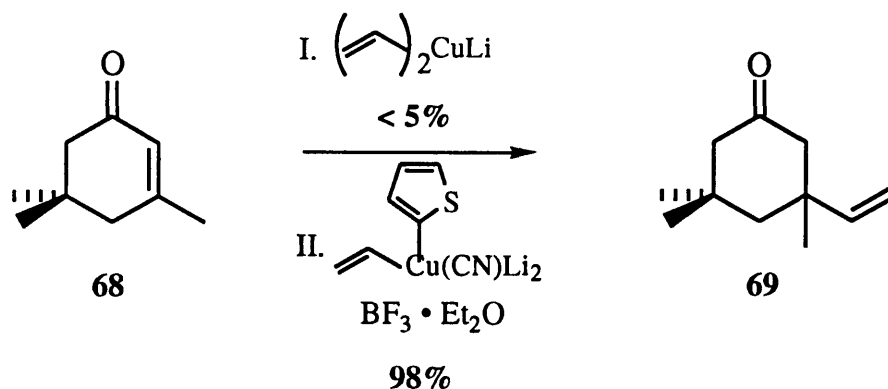
⁵⁹ Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

⁶⁰ (a) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.

⁶¹ (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; McMurry, J. F. *Acc. Chem. Res.* **1988**, *21*, 47.

Consequently, coupling of the cyclohexenone intermediate to side chain **66** required alternative means. 1,4-Addition of the aryl cuprate of side chain **66** to enol triflate **54** was attempted under various reaction conditions; however, each attempt resulted in a very low yield of photosubstrate **61**. Dialkyl cuprate addition resulted in less than 20% yield of the desired photosubstrate **61**, while the use of higher order cyanocuprates⁶² afforded less than 10% of the desired product. In both cases, significant amounts of diaryl products were isolated, resulting from the dimerization of the cuprate intermediates. It was hypothesized that the enol triflate was not activated towards the addition of the bulky aryl cuprate to the substituted β position of the enone.

Lipshutz⁶³, in previous attempts of the 1,4-addition of vinyl cuprates to isophorone **68** (Scheme 27), encountered a similar problem. Addition of dialkyl or higher order



Scheme 27: Lewis acid activated cuprate addition using a non-transferable thienyl ligand.

cyanocuprates resulted in less than 5% of the desired 1,4-addition product **69**. It was postulated that the enone was not activated towards the addition of the cuprate to the substituted β position of the enone. He found that the addition of boron trifluoride dietherate to the cuprate mixture resulted in greater than 98% yield of the desired β

⁶² Lipshutz, B.H. *Tetrahedron Lett.* **1983**, 24, 127.

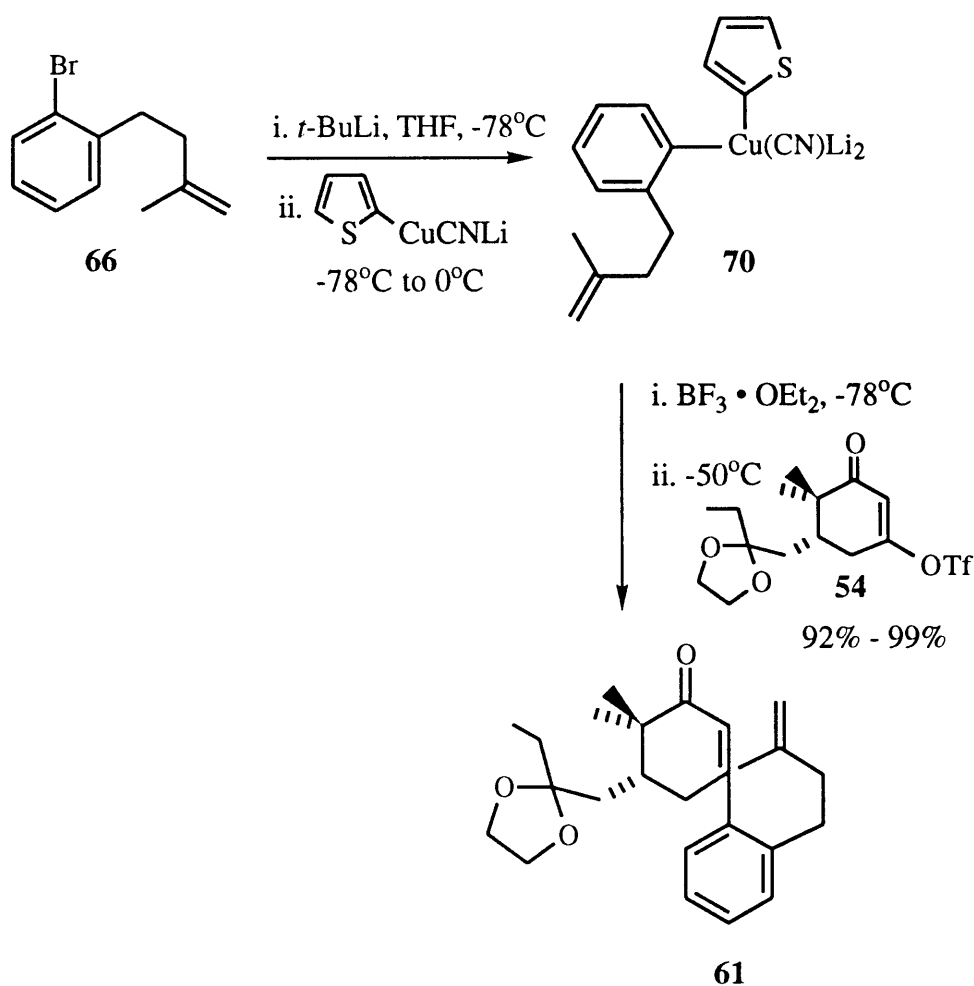
⁶³ Lipshutz, B. H., Parker, D. A.; Kozlowski, J. A.; Nguyen, S.L. *Tetrahedron Lett.* **1984**, 52, 5959.

disubstituted product. Additionally, thiophene could be used as a non-transferred ligand without lowering the yield of the reaction.

Whether the use of boron trifluoride would be helpful in our system was questionable, because it had not been used in couplings where additional atoms with free lone pairs were present. It was possible, in our system, that the boron trifluoride would complex to the oxygen lone pairs on the ketal, therefore causing removal of this protecting group, as it was known that boron trifluoride dietherate readily removes the ethylene ketal protecting groups.⁶⁴ Unlikely, however, was the complexation of the boron trifluoride to the oxygens present in the trifluoromethylsulfonate group due to its electron withdrawing nature.

Fortunately, boron trifluoride dietherate served to successfully activate enol triflate **54** to the 1,4-addition of cuprate **70** in 92-99% yield (Scheme 28). For the reaction, thiophene was deprotonated with *n*-butyllithium at -78 °C and the reaction was warmed to 0 °C and was stirred for 1 hour. The formation of the thienyl cuprate was completed by addition of cuprous cyanide at -78 °C and stirring at room temperature for 20 minutes. It was found that halogen metal exchange of the aryl bromide was best accomplished by two equivalents of *tert*-butyllithium. Cuprate **70** was prepared by transferal, via cannula, of the aryl lithium compound into the thienyl cuprate mixture. This solution was warmed to -50 °C before the addition of boron trifluoride dietherate at -78 °C, followed by the addition of enol triflate **54** at -50 °C. The reaction occurred immediately at -50 °C, and after workup and isolation via flash column chromatography, a 92-99% yield of photosubstrate **61** was afforded.

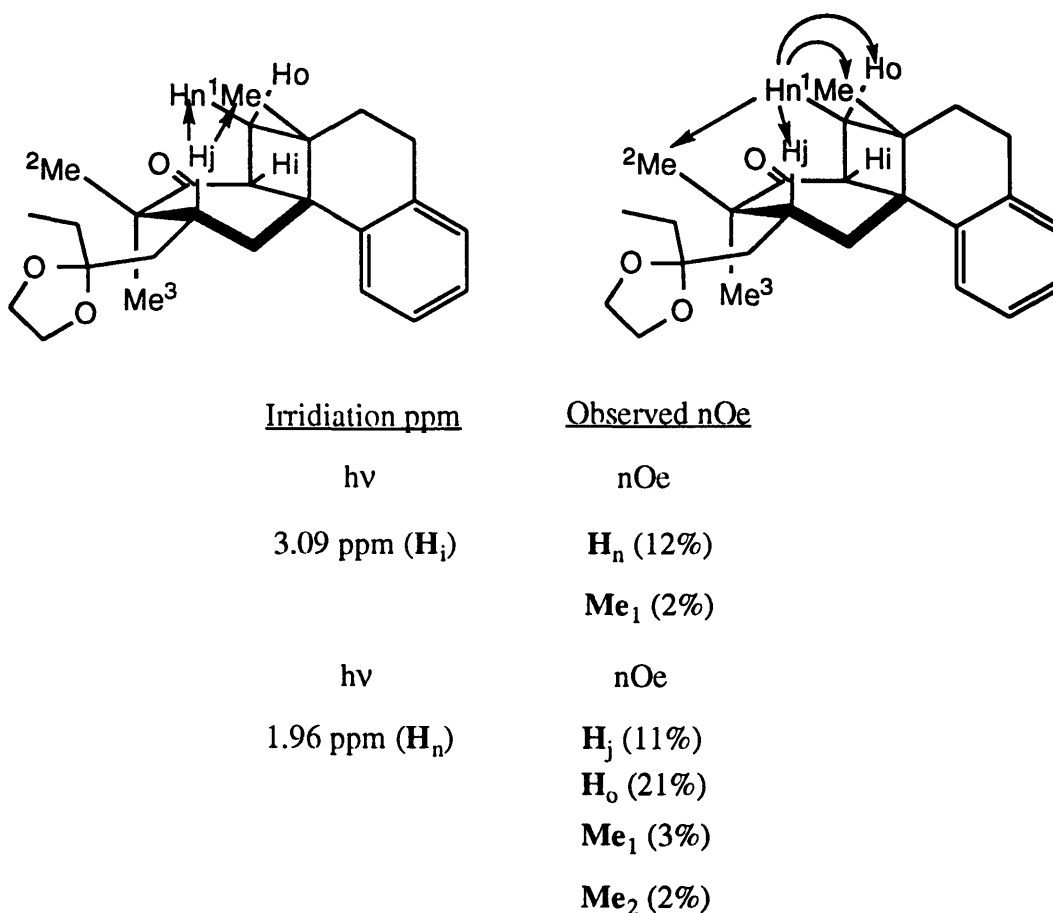
⁶⁴ Greene, T. A.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed. John Wiley and Sons, Inc., 1991, pg. 306.



Scheme 28: Synthesis of photosubstrate **61**.

Photosubstrate **61** was cyclized under a variety of conditions, using varying solvent mixtures, temperatures, and apparatus. Reaction times were short -- ranging from 20-40 minutes, as opposed to the 5 hour reaction time of the previous system. Best yields were obtained using a triple-walled Pyrex immersion well and a solvent mixture of hexane and benzene at 0 °C. The use of a triple-walled immersion well served to multiply the filtering effect of Pyrex and, in combination with benzene, diminish the overphotolysis of the reaction mixture (discussed later). Under these conditions, the reaction afforded only one stereoisomer of the photoproduct in 80 - 90% yield. NOE difference experiments were performed on this product in order to determine the stereochemistry of the only isolated

stereoisomer (Scheme 29). During these experiments, upon irradiation of the C(1) methine proton (H_j) a twelve percent nOe was observed to the cyclobutane proton H_n , and a two percent nOe was observed to the cyclobutane methyl group, Me_1 . When H_n was irradiated, an eleven percent nOe was seen to H_j , a twenty-one percent nOe was seen to H_n 's geminal partner H_o , a three percent nOe was seen to the cyclobutane methyl group, Me_1 , and a two percent nOe was seen to the β -geminal methyl group α to the ketone, Me_2 .

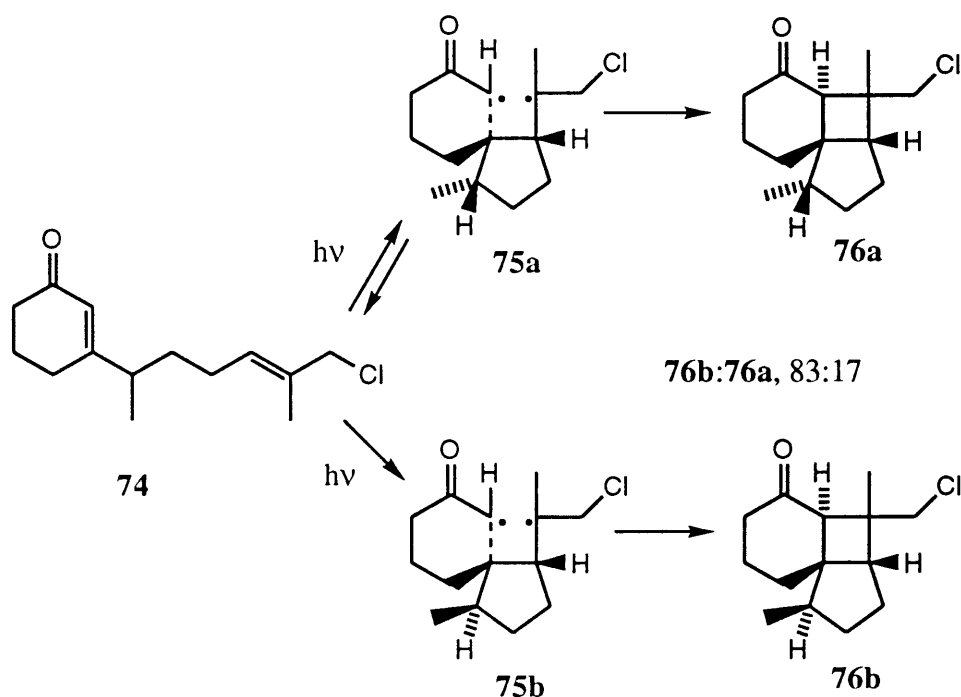


Scheme 29: Analysis of 1H - 1H nOe difference experiment for Photoproduct **62**.

These experiments, through modeling analysis, and comparison to the previous nOe difference experiments, definitively determined that the only isomer obtained in the

photocyclization was, in fact, the desired isomer **62** which bore the correct stereochemistry of the C(8) methyl substituent.

Consequently, the addition of an aromatic moiety to the side chain of the photocyclization substrate causes an unprecedented reversal in facial selectivity of the enone in the intramolecular enone-olefin system. A close examination of this reaction suggests a complex array of factors determining the reversal of stereochemistry. A search of the literature reveals a relevant reaction by Oppolzer in the intramolecular enone-olefin photocyclization of enone **74** (Scheme 30).⁶⁵ For this reaction, Oppolzer invokes the

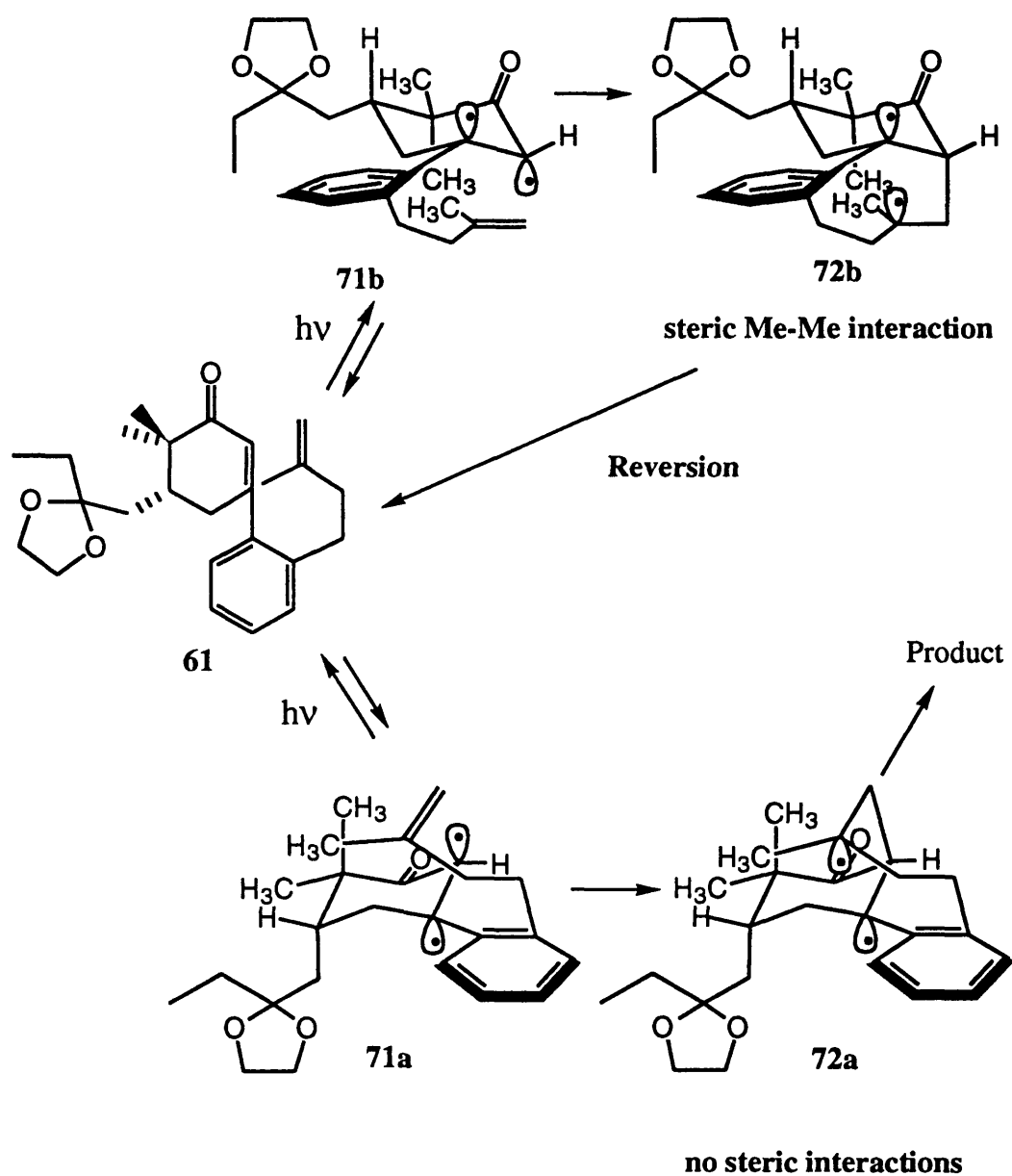


Scheme 30: Oppolzer's rationale invoking the product development control theory.

theory of product development control to explain the stereochemical outcome of this system, where it states that the rate of partitioning between the two intermediate 1,4-diradicals (**75a** and **75b**) is different. Diradical **75a**, which leads to the minor isomer, is thought to proceed slowly to cyclobutane **76a** because of steric interactions between the

⁶⁵ Oppolzer, N.; Zutterman, F.; Battig, K. *Helv. Chim. Acta.* **1983**, *66*, 322.

secondary methyl group and the hydrogen α to the carbonyl during the formation of the final cyclobutane carbon-carbon bond. Consequently, radical reversion is the predominant reaction of intermediate **75a**. Because the steric interaction is absent in intermediate **75b**,



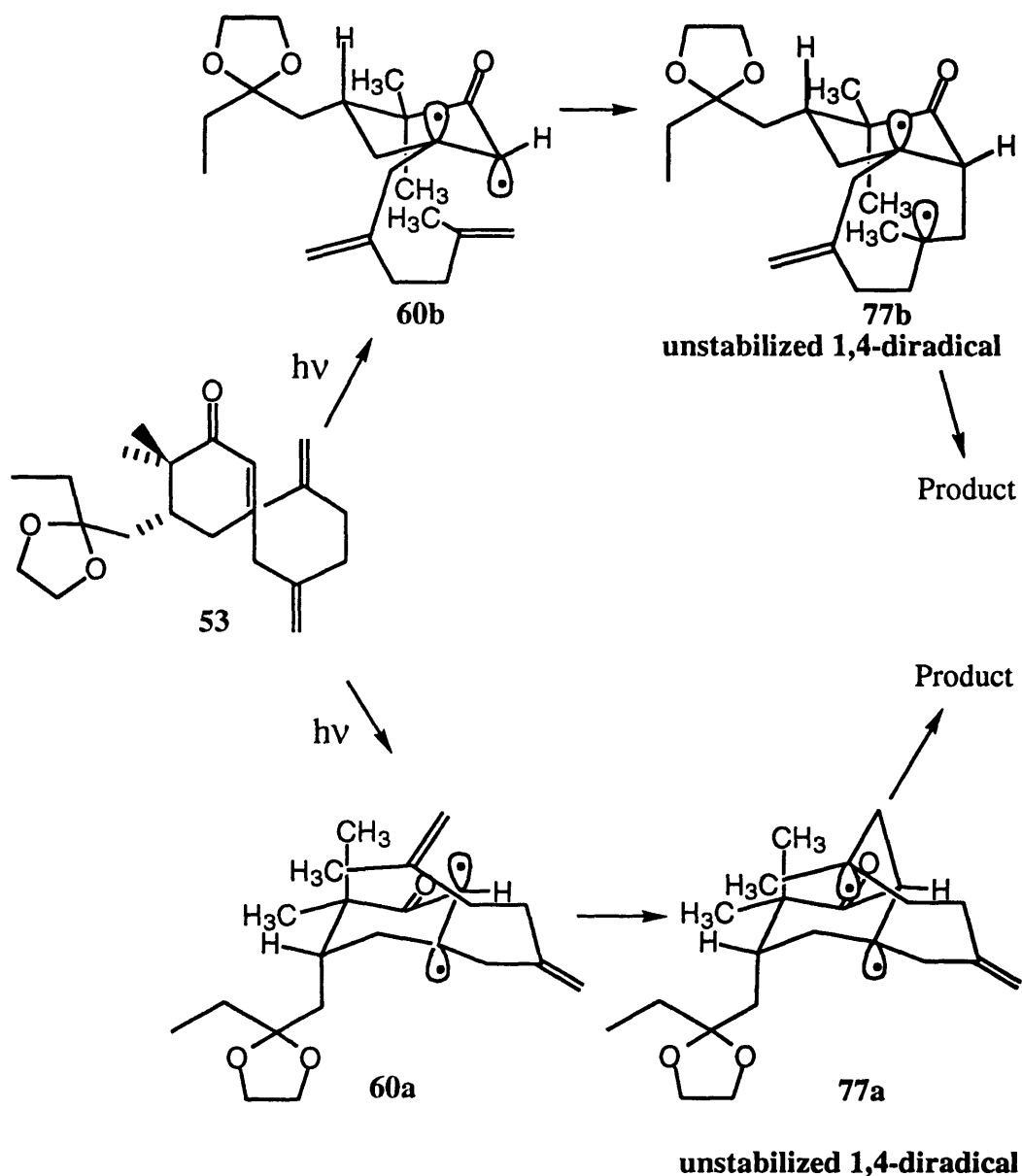
Scheme 31: Comparison of reactive intermediates in the photocyclization of photosubstrate **61**.

the diradical proceeds smoothly to product. The resulting product is therefore assumed to be a result of thermodynamic preference for the major product.

Oppolzer's theory can be applied to our system to explain the stereochemical preference for the photocyclization of enone **61**. In order to analyze this hypothesis, the 1,4-diradicals which are formed after the creation of the first carbon-carbon bond α to the carbonyl group must be compared (Scheme 31). As previously stated, in the mechanism for the photocyclization, following the formation of the carbon-carbon bond α to the ketone, a 1,4-diradical triplet results. In order for the formation of the second cyclobutane bond to occur, flipping of the triplet spin must first take place. This final bond formation proceeds slowly in the 1,4 diradical system **72b**, which leads to the formation of the undesired product, because of the steric interactions between the α -geminal methyl group and the methyl group on the olefin. Consequently, reversion is the predominant pathway for intermediate **72b**. Because there are no such steric interactions present in intermediate **72a**, which leads to the formation of desired photoproduct, the reaction proceeds smoothly to the cyclobutane compound.

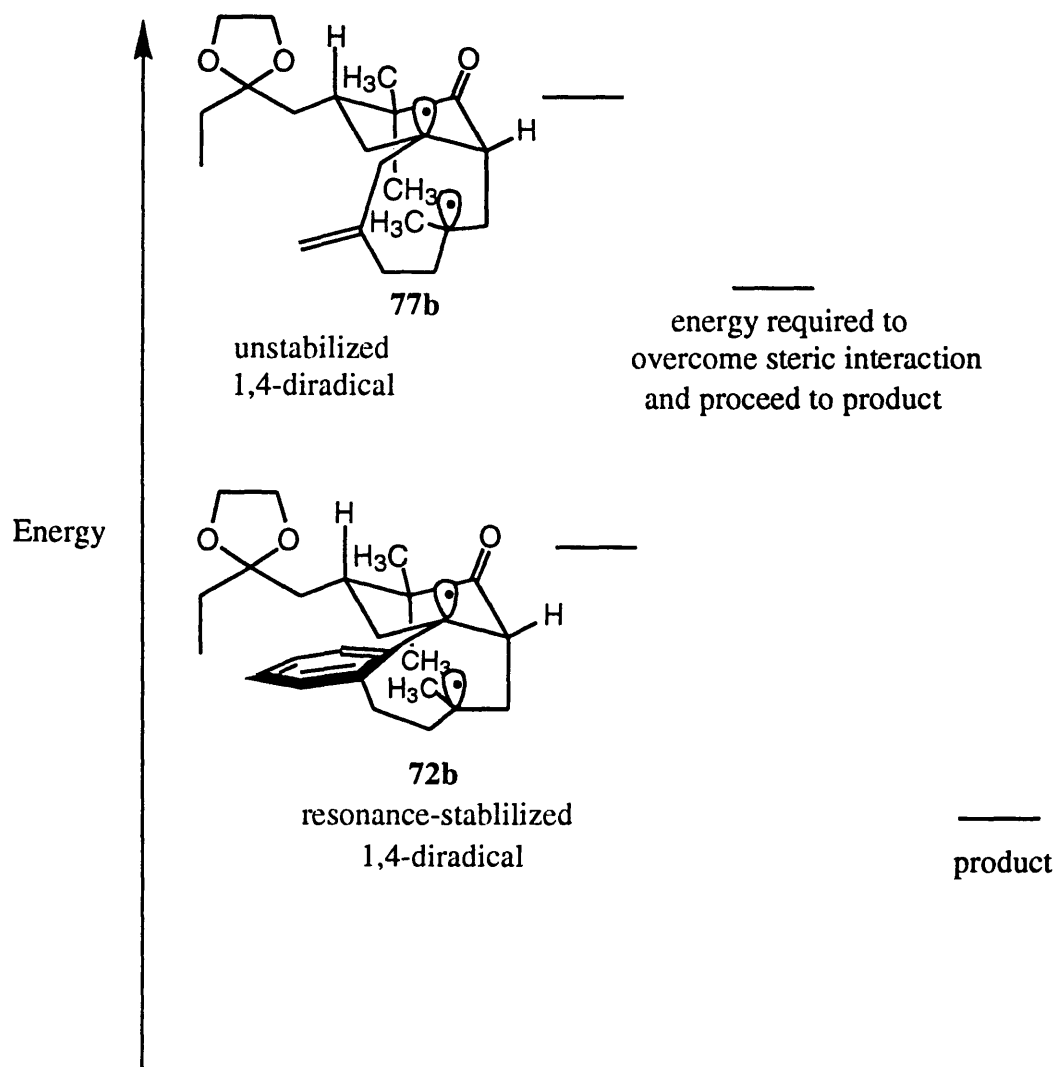
While this analysis is satisfying in that it explains the stereochemical outcome of the photocyclization of aromatic-substituted enone **61**, it does not explain the differences in this cyclization and that of the simple-olefin-substituted enone **53**. In order to understand these differences, 1,4-diradical **72b** (Scheme 31) and 1,4 diradical **77b** (Scheme 32) must be compared. Diradical **77b** (Scheme 32), which is an intermediate of the cyclization of the simple olefin photosubstrate **53**, is a high energy intermediate resulting from the absence of resonance stabilization of either of the radicals. Although the methyl-methyl steric interaction is present in this intermediate, the amount of energy that is required to overcome this interaction is insignificant compared to the energy of the diradical system. Therefore, spin flip and formation of the second cyclobutane bond is a downhill process. Since the aromatic ring stabilizes the benzylic radical present in intermediate **72b** (Scheme 31), spin flip and collapse of the diradicals does not occur spontaneously. The presence of

the aromatic ring lowers the energy of the 1,4-diradical intermediate; therefore, the inherent high energy steric interaction between the C(8) methyl and the C(15 α) methyl creates a high barrier to spin flip and subsequent bond formation, resulting in overall reversion to the ground state as opposed to product formation. Since no steric interactions are present in intermediate **72a**, the barrier to the second bond formation is lower, resulting in product formation.



Scheme 32: Analysis of triplet 1,4-diradicals in the simple olefin system.

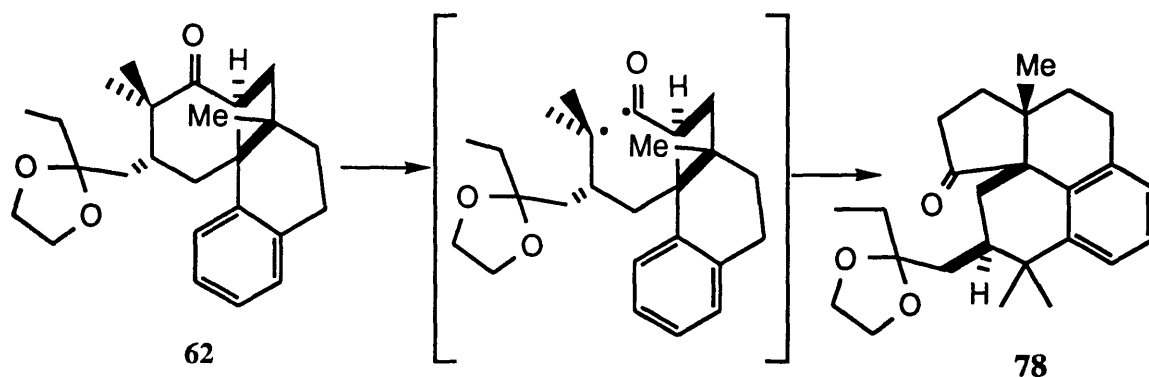
This explanation can be simplified when it is viewed graphically (Scheme 33). Since diradical **77b** possesses more energy than what is required to overcome the steric interactions, the final steps occur spontaneously. However, because of resonance stabilization, **72b** possesses less energy than what is required to overcome the energy barrier leading to product formation; consequently, reversion predominates.



Scheme 33: Graphical representation of relative energy barriers.

The amount of undesired isomer that was formed in the photocyclization of aromatic-substituted enone **61** was difficult to quantify, this compound was never isolated or viewed spectroscopically. Efforts were undertaken to both isolate the undesired isomer and to observe its presence in the ^1H NMR; but these attempts were unsuccessful. Nevertheless, we do not assume that none of the undesired isomer is being formed. This is because the crude ^1H NMR is complicated by the presence of an overphotolyzed product (discussed later). It is known, however, that the heating of the reaction mixture to as high as $60\text{ }^\circ\text{C}$ does not result in any increased amounts of the undesired isomer, as this heating still does not result in the observation of the undesired isomer.

An additional product is consistently isolated from the product mixture of the photocyclization of substrate **61**, and ^1H NMR analysis shows it to be the result of an initial Norrish Type I fragmentation of cyclobutane **62** (Scheme 34, compound **78**). This is not a surprising result, as *tert*-butyl ketones, especially cyclobutyl-*tert*-butyl ketones, readily undergo Norrish Type I reactions.⁶⁶ However, the usual course of a Norrish Type

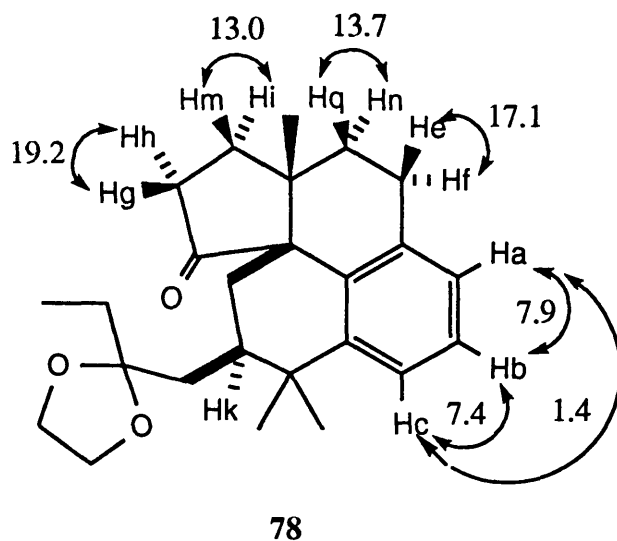


Scheme 34: Norrish type I product.

I reaction results from the homolytic cleavage between the carbonyl group and the *tert*-butyl group followed by a hydrogen abstraction by the carbonyl radical from one of the methyl groups. In our case, however, the ultimate product of the reaction is different.

⁶⁶ Swenton, J. S. *J. Chem Educ.* **1969**, *46*, 217.

This reaction is postulated to occur first through the homolytic cleavage of the bond between the carbonyl and the geminal methyl groups. Following this cleavage, three unique steps must occur: (1) ring expansion of the cyclobutane ring, (2) hydrogen abstraction of the aryl hydrogen, and (3) bond formation between the tertiary radical and the arene ring. The order of these mechanistic steps, however, is not known. Evidence observed in the ^1H NMR spectrum that supports the formation of compound **78** (Scheme 35) is: (1) the presence of only three aromatic protons -- the coupling pattern of which



coupled protons	coupling constants	coupled protons	coupling constants
H _g H _i	10.9 Hz	H _n H _e	11.3 Hz
H _g H _m	2.2 Hz	H _n H _f	6.3 Hz
H _h H _m	9.5 Hz	H _q H _f	4.0 Hz
H _h H _i	8.9 Hz	H _q H _e	6.1 Hz

Scheme 35: ^1H NMR evidence for Norrish type I product.

suggests they are all next to each other, (2) the disappearance of the geminal cyclobutane proton pair with the 12.9 ppm coupling, (3) the appearance of two sets of geminal pairs --

each coupled to one another, and (4) the presence of three geminal pairs, each coupled to either a methyl group or the methine proton H_K . Yields of overphotolyzed product **78** are dependent on solvent, apparatus, and mixing techniques. Performance of the reaction at $-78\text{ }^{\circ}\text{C}$ in hexane results in the maximum 20% of product **78** while performing the reaction in a mixture of hexane and benzene at $0\text{ }^{\circ}\text{C}$ results in the minimum of 5% of the overphotolyzed product. The efficiency of mixing techniques also have an influence on the amount of over-photolyzed product that is isolated -- when poor mixing was achieved, a higher percentage of tetracycle **78** is formed.

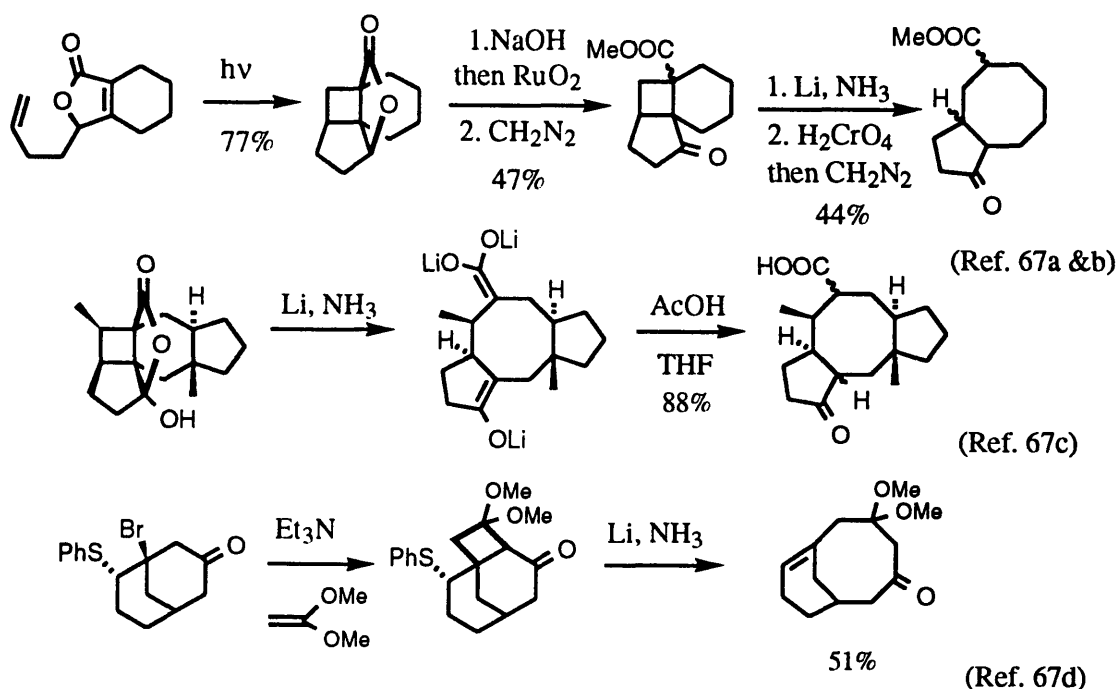
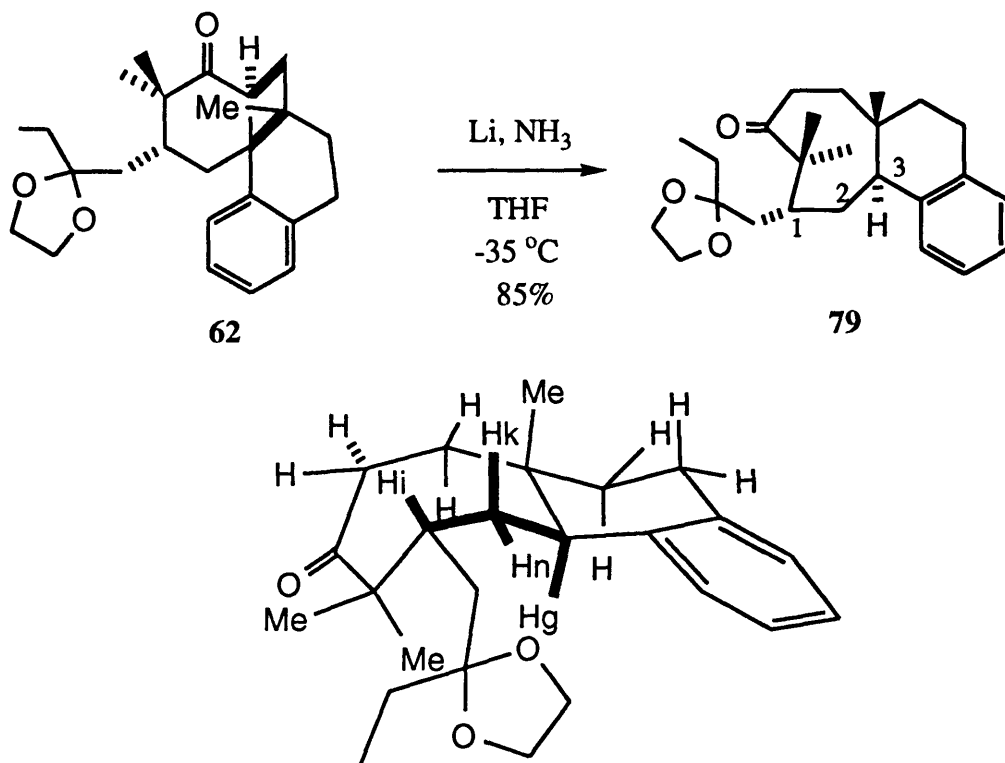


Figure 2: Previous cyclobutane fragmentations using Li/NH_3 .

Now that the stereochemistry at the C(8) position was correctly established, the next challenge was to cause the fragmentation of the cyclobutane ring, while setting the stereochemistry at the C(3) position, thus establishing the *trans*-ring juncture of the B-C ring system. Fragmentation of cyclobutanes had previously been performed on cyclobutyl-

1,4-dicarbonyl compounds to create cyclooctanone systems⁶⁷ (Fig. 2) which formed, in many cases, the more thermodynamically stable stereoisomer.⁶⁸ However, there were many exceptions to this observation.⁶⁹



coupled protons	coupling constants
H _g H _k	13.1 Hz
H _g H _n	3.1 Hz
H _k H _i	4.4 Hz
H _n H _i	12.3 Hz

Scheme 36: Cyclobutane fragmentation and ¹H NMR evidence for its stereochemical outcome.

⁶⁷ (a) Baker, W. R.; Senter, P.D.; Coates, R. M. *J. Chem. Soc. Chem. Commun.* **1980**, 1011. (b) Coates, R. M.; Baker, W. R.; Senter, P. D. *J. Org. Chem.* **1982**, *47*, 3597. (c) Coates, R. M.; Muskopf, J. W.; Senter, P. D. *J. Am. Chem. Soc.* **1985**, *107*, 3541. (d) Kraus, G. A.; Thomas, P. J.; Hon, Y. S. *J. Chem. Soc. Chem. Commun.* **1987**, 1849.

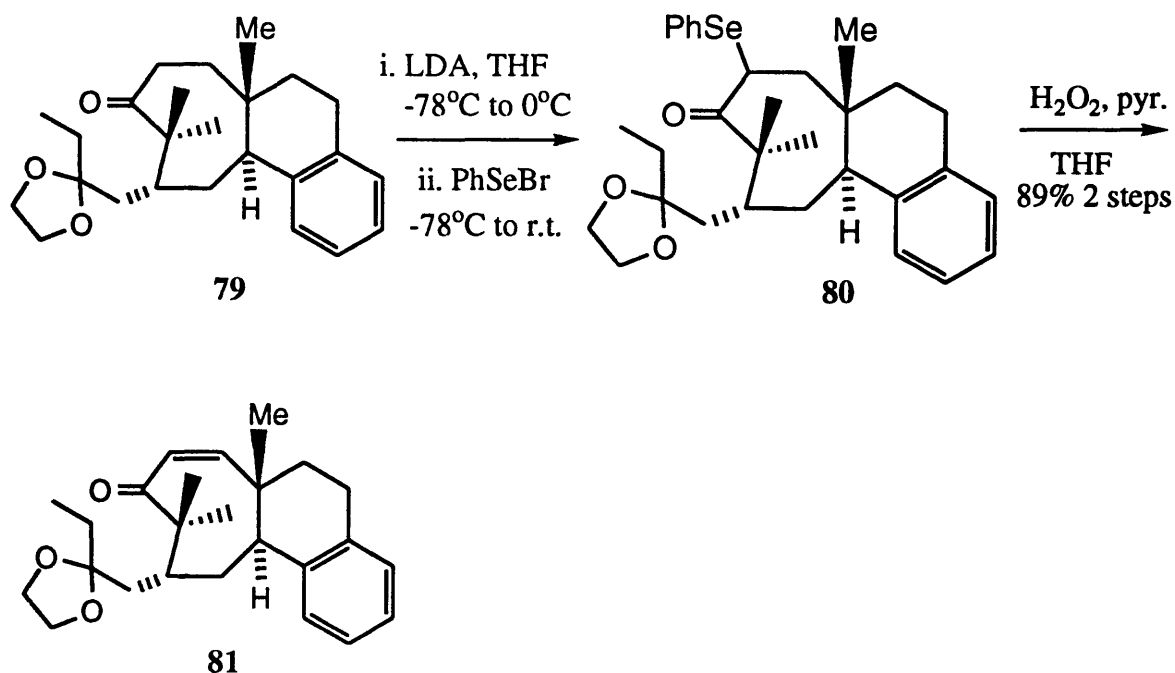
⁶⁸ (a) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3054. (b) *Org. React.* **1976**, *23*, 1.

⁶⁹ Stork, G.; Darling, S. D.; *J. Am. Chem. Soc.* **1960**, *82*, 1512. (b) Stork, G.; Darling, S. D.; *J. Am. Chem. Soc.* **1964**, *86*, 1761.

Therefore, fragmentation of cyclobutyl ketone **62** was accomplished via dissolving metal conditions (Scheme 36), using a slight excess of lithium metal in liquid ammonia at $-33\text{ }^{\circ}\text{C}$. Spectral analysis (^1H NMR) gave evidence suggesting that the fragmentation occurred with the desired stereochemistry at the C(3) position. This evidence was detected in the observed couplings between the proton at the newly-formed C(3) ring-juncture (H_g), and the protons at the C(2) position (H_k and H_n), along with the observed couplings between the protons at the C(2) position and the methine proton at the C(1) position (H_i). These couplings suggested, through an analysis of dihedral angles, that H_g and H_k were nearly 180° from each other, as evidenced by the large, 13.1 Hz, coupling constant, while H_g and H_n were nearly 60° apart, as suggested in their small, 3.1 Hz coupling. Furthermore, H_n and H_i were almost 180° from each other, as seen in their large, 12.3 Hz, coupling constant, while H_k and H_i were nearly 60° apart as evidenced in their small, 4.4 Hz coupling. Attempts to gather further evidence as to the stereochemistry of the B-C ring juncture through nOe difference experiments were inconclusive.

With the presumably desired intermediate tricycle **79** in our possession, it was desirable to ascertain if useful chemistry could be performed on the B-ring (Scheme 37). Toward this goal, intermediate **79** was transformed into α -phenylselenenylketone **80** with lithium diisopropylamide and phenylselenium bromide.⁷⁰ The resulting selenenyl compound **80** was isolated as a single isomer; however, the stereochemistry of the molecule was not determined. Elimination of selenide **80** was smoothly accomplished through oxidation to the selenoxide with hydrogen peroxide in tetrahydrofuran and pyridine, which readily underwent elimination at room temperature, to yield enone **81** in 89% from ketone **79**.

⁷⁰ (a) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.



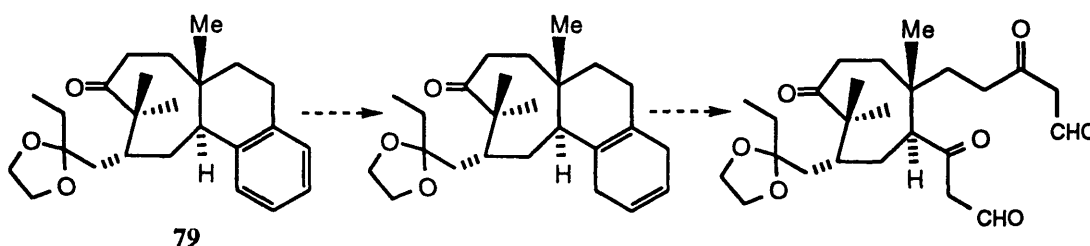
Scheme 37: Elaboration of tricycle **79**.

Attempts to cause the epoxidization of enone **81** nucleophilically with *tert*-butyl hydroperoxide and Triton B⁷¹ were unsuccessful. These experiments were investigated more extensively on methoxy analogs described in the next section.

⁷¹ (a) Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 651. (b) Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3.

3.3 Synthesis of Methoxy Analogs

A summary of the knowledge gained from the studies on the newly designed aromatic system showed that the addition of the aromatic moiety not only established the correct C(8) stereochemistry, but it also allowed for the facile fragmentation of the cyclobutane carbocycle to create the desired *trans* -ring fusion between the B and C rings. At this point in the project, however, a dilemma was faced. The presence of an aromatic ring in the molecule, created the necessity to excise three carbons in order to establish the C-ring functionality in taxusin. It was envisioned that cleavage of the aromatic ring could be accomplished through a Birch reduction⁷² followed by oxidation of the resulting diene with ozone to form a 1,3-dicarbonyl compound. Unfortunately, reduction and oxidation of our unsubstituted system would result in an undesirable cleavage of the newly-formed C-ring (Scheme 38); however it was tempting to continue on the synthetic pathway with the

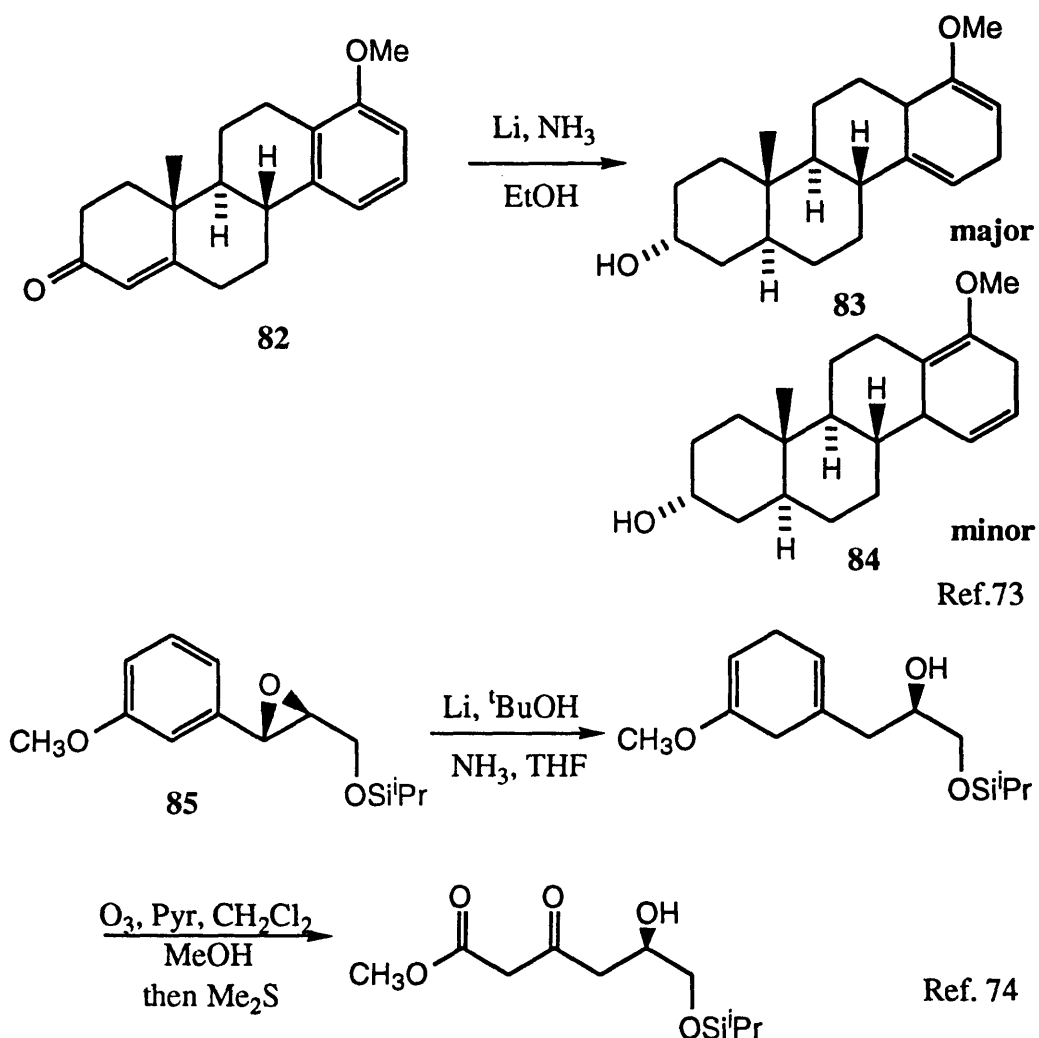


Scheme 38: Regiochemical preference for Birch reduction of non-substituted aromatic rings.

model, unsubstituted aromatic system, using the material in our possession to work out the ensuing synthetic steps. There was no guarantee, however, that once the synthetic steps

⁷² (a) Birch, A. J.; Subba Rao, G. *Adv. Org. Chem.* **1972**, 8, 1. (b) Harvey, R. G. *Synthesis* **1980**, 161. (c) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, 3, 35. (d) Rabideau, P. W. *Tetrahedron* **1989**, 45, 1599.

were optimized on the unsubstituted system, these reactions would be successful on a useful, substituted system. Consequently, it was decided that it was best to design a system that could result in a useful cleavage of the aromatic ring, and use the actual system to perform the actual synthetic steps.

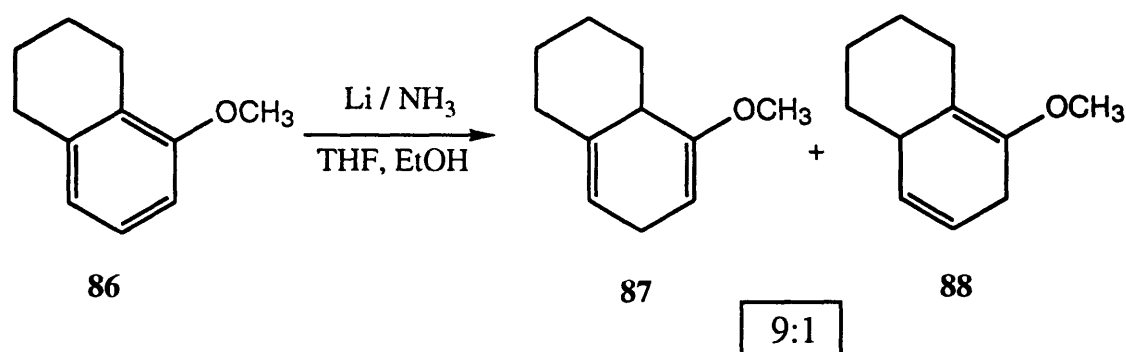


Scheme 39: Precedent for Birch reduction regiochemistry.

A careful placement of substituents onto the aromatic ring was necessary to create a diene that would result, when oxidized, in a 1,3-dicarbonyl that could be elaborated into the

functionality of the taxusin C-ring. Also desirable was a system that could be attained through a short, synthetic sequence. It was anticipated that an α -anisole system would be useful toward this end. In his synthesis of *epi*-androsterone **82** (see Scheme 39), Johnson⁷³ found that an α -anisole system could be reduced with lithium metal in liquid ammonia to afford, as a major product, diene **83** with diene **84** being isolated as a minor isomer. More recently, in his synthesis of β -ketoesters, Evans⁷⁴ used a similar anisole assemblage **85** as a protective group for this sensitive functionality which was deprotected via Birch reduction followed by ozonolysis. Therefore, it was foreseen that this system would be one that could be incorporated into our synthesis and could be later elaborated into the functionality found on the C-ring of taxusin.

Although Johnson, in his synthesis of *epi*-androsterone reported that diene **83** was isolated as the major isomer, he did not report a ratio for **83:84**. He did, however, state that the highest ratio of **83:84** was obtained when ethanol was used as the proton source.



Scheme 40: Model studies for Birch reduction regiochemistry.

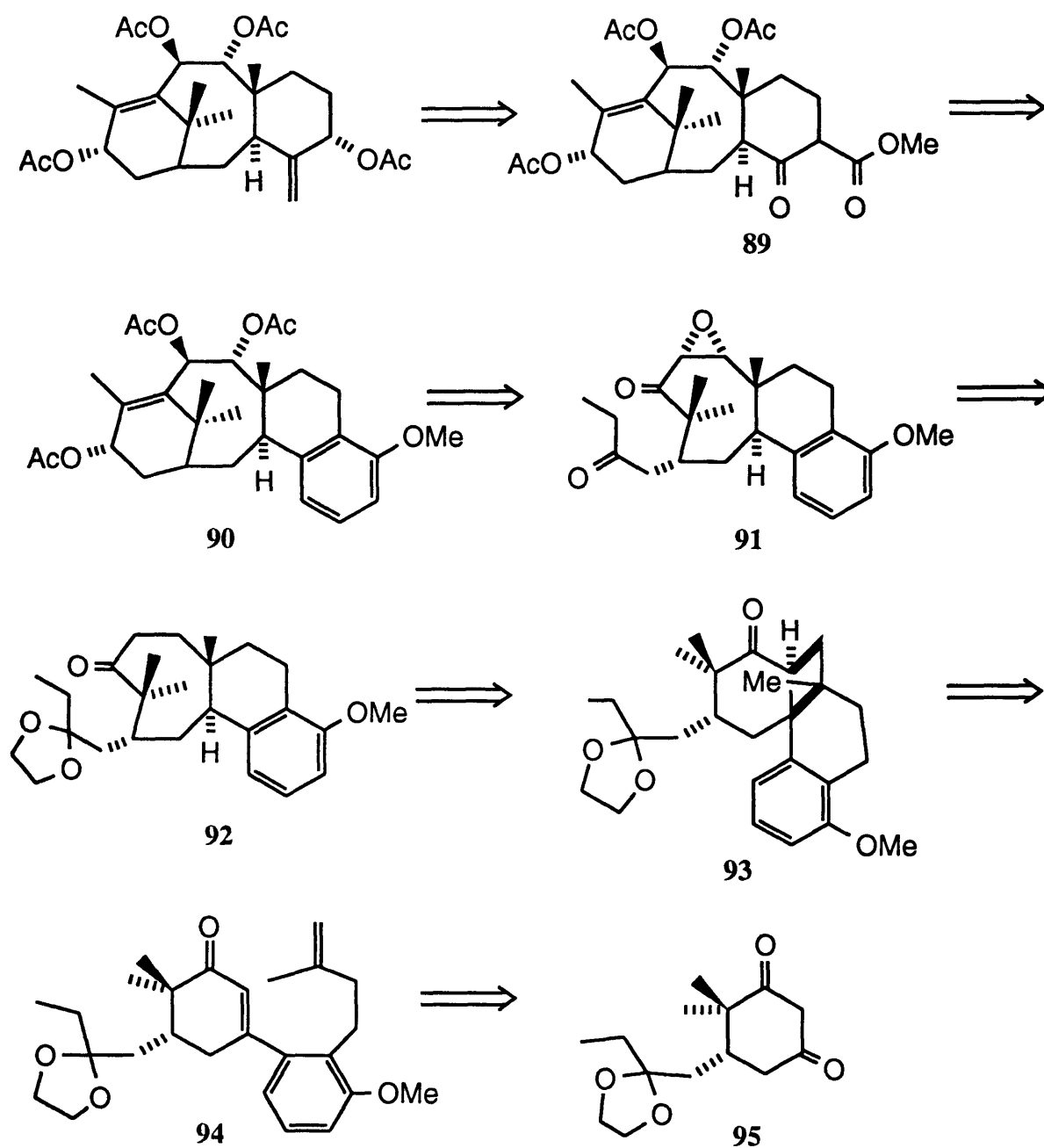
Therefore, it was desirable to quantify a regiochemical ratio for the reaction, because it was thought that if this ratio were low, the α -anisole assemblage would not be useful in our synthetic route. Model studies were performed on the 1-methoxy-5,6,7,8-

⁷³ Johnson, W. S.; Vrendenburg, W. A.; Pike, J. E. *J. Am. Chem. Soc.* **1960**, *82*, 3409.

⁷⁴ Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.

tetrahydronaphthalene system (**86**) shown in Scheme 40. When anisole **86** was subjected to dissolving metal conditions in the presence of ethanol, a 9:1 ratio of **87:88** was obtained in a 67% overall yield, with the remainder being isolated as recovered starting material.

With the presence of the new, anisole appendage, an updated synthetic plan for the construction of taxusin was necessary (Scheme 41). The first retrosynthetic step was the interconversion of the C-ring, the functionality of which was expected to be derived from β -ketoester **89** which was envisioned to be the result of a Birch reduction and oxidation performed on anisole compound **90**. β -Ketoester **89** was an attractive intermediate, because methodology for its conversion to the C-ring functionality was previously optimized in Holton's synthesis of *ent*-taxusin.¹⁷ Therefore, it was expected that the ester could be smoothly decarboxylated resulting in the ketone, from which formation of the silyl enol ether, epoxidation, and a Wittig reaction would result in the allylic acetate found in taxusin. From tetracycle **90**, in the retrosynthetic direction, the A-ring was the next disconnection, construction of which was expected to proceed smoothly through the tandem-aldol Payne rearrangement of epoxy diketone **91** which would be formed, in the synthetic direction, through oxidative and reductive transformations of ketone **92**. From ketone **92**, the next disconnection was the C(3)-C(10) connective transform to form cyclobutane intermediate **93** which was expected, in the forward direction, to be the result of an enone-olefin [2+2] photocyclization of photosubstrate **94**, the stereochemical outcome of which was expected to be similar to that for the unsubstituted photosubstrate **61**. Photosubstrate **94** was anticipated to be formed through the coupling of a derivative of the key intermediate, diketone **41**.

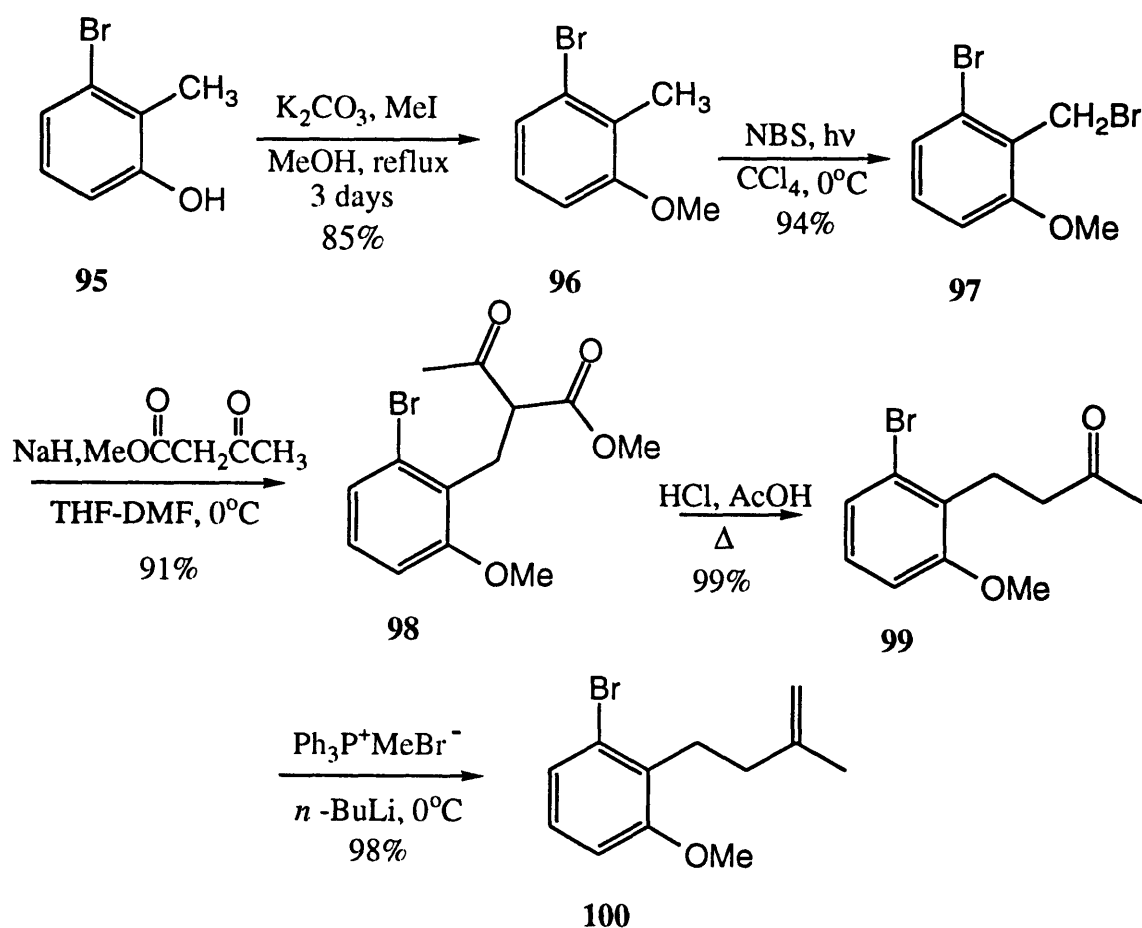


Scheme 41: Updated synthetic plan for the construction of taxusin.

The synthesis of bromo-anisole side chain **100** (see Scheme 42) began with 3-bromo-2-methylphenol (**95**) which was prepared in two steps from 1-bromo-5-nitrotoluene according to the method by Cresp, *et al.*⁷⁵ Methylation of 3-bromo-2-methyl phenol (**95**)

⁷⁵ Cresp, T. M.; Giles, R. G. F.; Sargent, M. V. *J.Chem.Soc. Perkin I* **1974**, 2435.

was accomplished through a reaction with iodomethane and potassium carbonate in methanol which was heated at reflux for three days⁷⁶ to form 3-bromo-2-methylanisole (**96**) in 85% yield. Bromination of the benzylic position was smoothly accomplished with *N*-bromosuccinimide which was activated by irradiation with a sun lamp to give a 94% yield of 3-bromo-2-(bromomethyl)anisole (**97**).⁷⁵ Benzyl bromide **97** was then alkylated with the sodium anion of methyl acetoacetate at 0 °C to afford β -ketoester **98** which was readily dealkoxycarbonylated with hydrochloric acid in acetic acid to result in the formation

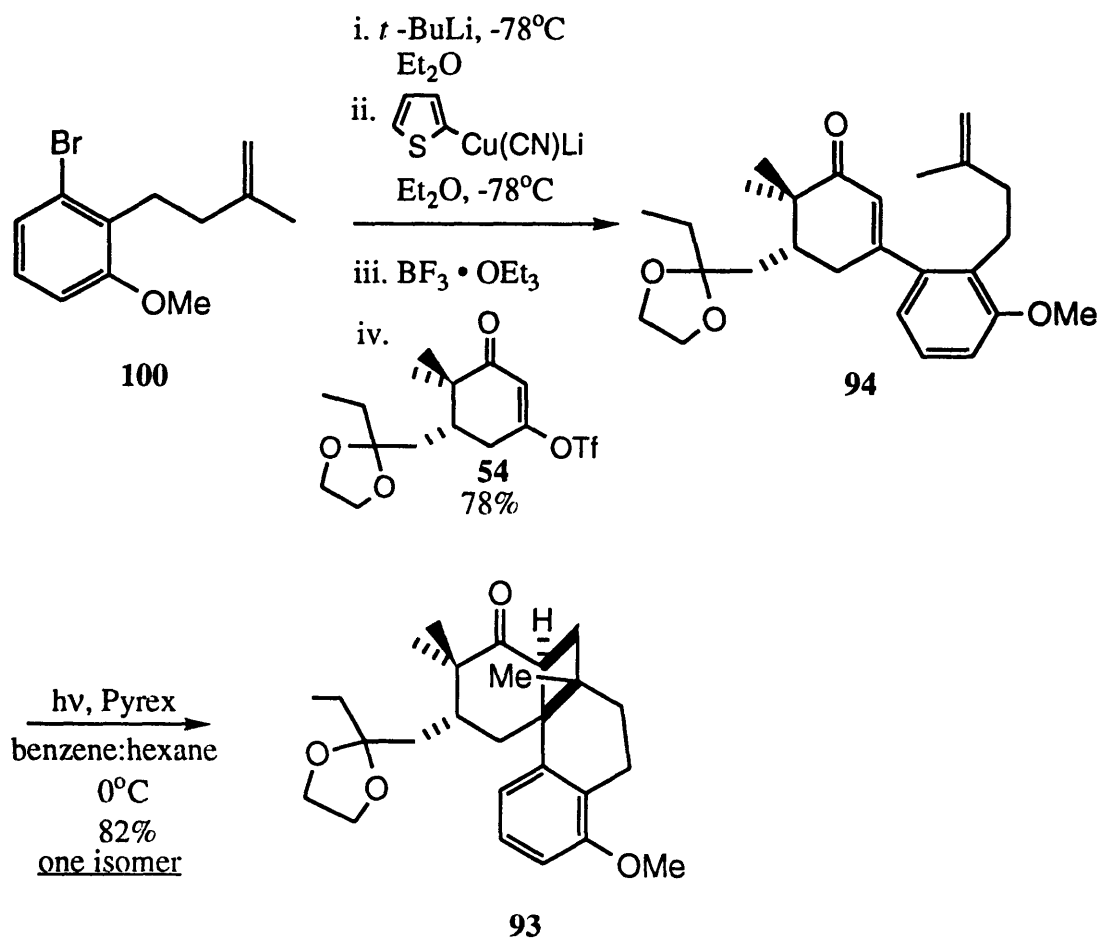


Scheme 42: Synthesis of anisole side chain.

⁷⁶ Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098.

of ketone **99** in quantitative yield. Alkylation, in this case, was accomplished with methyl acetoacetate, because dealkoxycarbonylation of the ethyl ester corresponding to compound **98** via Krapcho conditions resulted in an unacceptable 32% yield of ketone **99**. Completion of the synthesis of bromo-anisole side chain **100** was accomplished from ketone **99**, with methyltriphenylphosphonium bromide and *n*-butyllithium. This reaction sequence could be performed on a large scale beginning with 25 g of 1-bromo-5-nitrotoluene, to afford, after a seven step sequence, a 51% overall yield of anisole side chain **100**.

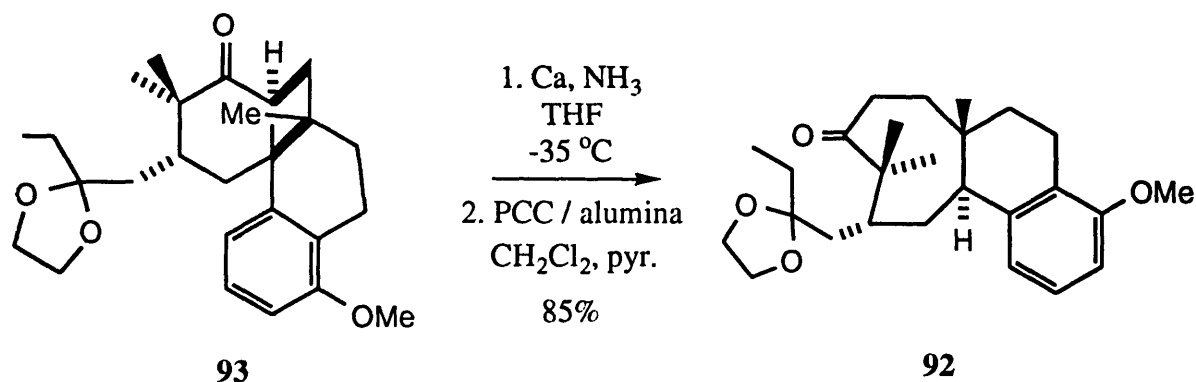
Cuprate addition of bromo-anisole side chain **100** to enol triflate **54** proved to be further complicated by the presence of the methoxy substituent. Presumably due to the electron donating nature by the methoxy substituent to the aromatic ring, first attempts at the cuprate addition resulted in large amounts of the aryl dimer formation. Corresponding yields of the methoxy-photosubstrate were low (15 - 25%). In his paper on the Lewis acid activation of enones in 1,4 cuprate additions, Lipshutz discussed the necessity of one equivalent of boron trifluoride dietherate per equivalent of enone.⁶² It was hypothesized that, in our system, the methoxy substituent could complex the Lewis acid, rendering it unavailable for enone activation. Therefore, problems leading to photosubstrate **94** were solved by altering the previous procedure for the addition of the thienyl cuprate to the Lewis acid activated enol triflate in the follow manner: (1) the reaction was performed on a large scale so water would not consume a large portion of the boron trifluoride, (2) lithiation of aryl bromide **100** was performed in a dilute solution of ether to lessen the chance of dimerization, and (3) 2.5 equivalents of boron trifluoride dietherate was used. With these alterations, a 78% yield of the photosubstrate **94** was isolated (see Scheme 43). Further optimization could possibly be obtained by increasing the amount of boron trifluoride dietherate added to the reaction; however, this was not attempted in fear that the ketal might be removed with such a large excess of Lewis acid.



Scheme 43: Formation of methoxy-substituted cyclobutane intermediate.

Photosubstrate **94** was irradiated with a 450 Watt, medium pressure, Conrad-Hanovia immersion lamp through a triple-walled Pyrex immersion well in a 5:1 solution of hexane:benzene at 0°C , and 82% of photoproduct **93** was isolated as a single diastereomer. Analysis of the obtained isomer via ^1H NMR, ^{13}C NMR, and IR proved it to be completely analogous to the non-methoxy substituted photoproduct **62**; therefore, it was assumed that photoproduct **93** was the desired stereoisomer. A compound analogous to the overphotolyzed product **78** was also observed; however, steps to minimize this product were taken as was previously mentioned.

Fragmentation of photoproduct **93** was first attempted using lithium metal and liquid ammonia, as was previously described. In this case, however, a mixture of unreduced cyclobutane **93**, reduced cyclooctanone **92**, and the corresponding over-reduced alcohol were isolated; therefore, calcium metal, which only resulted in a mixture of cyclooctanone **92** and the over-reduced alcohol, was employed (Scheme 41). The obtained

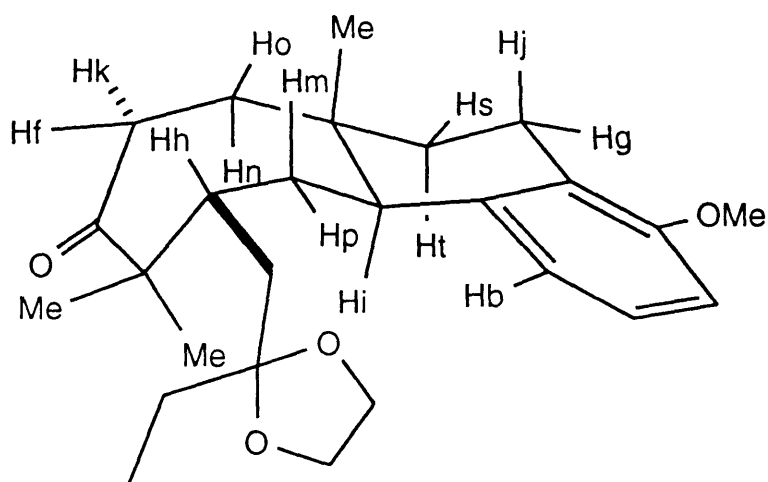


Scheme 44: Fragmentation of photoproduct **93**.

mixture was then subjected to pyridinium chlorochromate on neutral alumina to afford cyclooctanone **92** in 85% yield from photoproduct **93**.

Further evidence was desired, at this point, determining the stereochemistry of the B-C ring-juncture in cyclooctanone **92**; therefore, nOe difference experiments were performed (see Scheme 45). When the ring juncture proton (H_i) was irradiated, a 3% nOe was seen to aromatic proton H_b , a 2% nOe was seen to C(9 α) proton H_n , and a 2% nOe was seen to the C(2 α) proton H_p . When the C(7 α) proton (H_t) was irradiated, a 4% nOe was seen to H_i , a 3% nOe was seen to C(6 α) proton H_g , a 6% nOe was seen to C(9 α) proton H_n , and a 6% nOe was seen to its geminal partner H_s . When H_s was irradiated, a 3% nOe was seen to the C(8) methyl group, known to be β , a 3% nOe was seen to C(6 β) proton H_j , and a 7% nOe was seen to the C(9 β) proton H_o . Finally, when the C(1) methine proton H_h was irradiated, a 6% nOe was seen to the C(8) methyl, and a 3% nOe

was seen to the C(2 β) proton H_m. Through modeling analysis of the observed nOe evidence, the B-C ring juncture was definitively determined to be *trans*.



Irradiated ppm	Observed nOe	Irradiated ppm	Observed nOe
2.53 ppm (Hi)	H _b (3%) H _n (2%) H _p (2%)	1.48 ppm (Hs)	Me ₁ (3%) H _j (3%) H _o (7%)
1.39 ppm (Ht)	H _i (4%) H _g (3%) H _n (6%) H _s (6%)	2.60 (Hh)	Me ₁ (6%) H _m (3%)

Scheme 45: Analysis of nOe difference experiment of cyclooctanone **92**.

Chapter 4. Efforts Toward the A-ring Annulation of the *trans*-BC Ring System

4.1 Efforts Toward the Tandem-aldol Payne Rearrangement

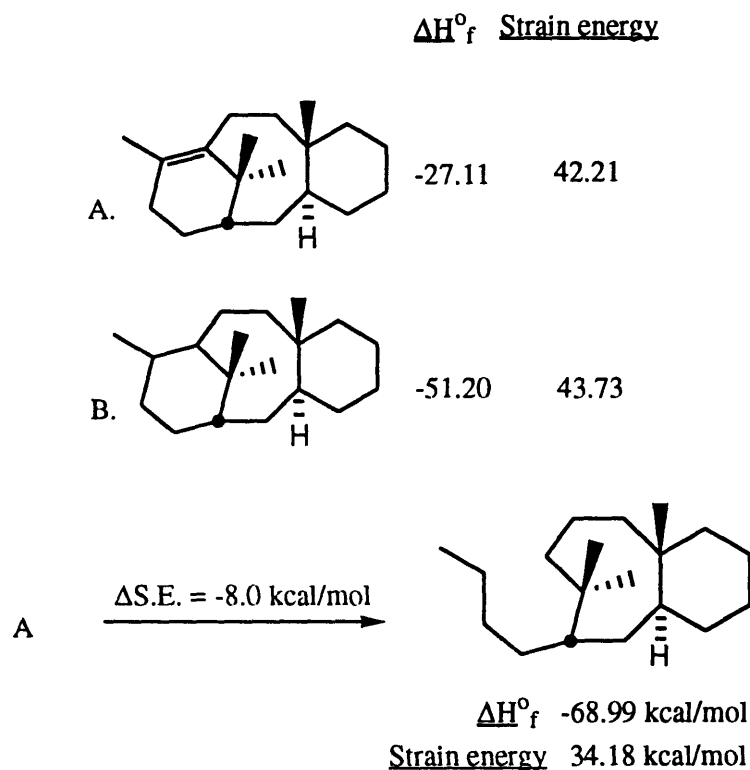
At this point in the synthetic strategy, a useful side chain had been synthesized and coupled successfully to a diketone derivative to form the desired photosubstrate. Photocyclization had been successfully performed to afford the desired diastereomer which incorporated the correct C(8) methyl stereochemistry found in taxusin. Finally, the cyclobutane compound resulting from the photocyclization had been successfully fragmented to yield the complete taxane B-C carbocyclic framework including the correct *trans*-B-C ring juncture.

The next challenge that was faced in the synthetic plan was that of the final cyclization -- the formation of the A-ring. Swindell, in his previous studies toward the synthesis of taxane molecules, also incorporated as a final cyclization, the closure of the A-ring.³¹ Before embarking on his synthesis using this A-ring annulation as one of the ultimate steps, calculations were performed on this system in order to ascertain if this reaction would be favorable. This is because he initially thought that the bridgehead olefin might possess a high amount of strain energy causing the planned aldol closure to be energetically disfavored. However, an analysis of the A-ring annulation of the bicyclo[6.4.0]dodecane *trans*-fused system suggested that this should be a favorable reaction. MM2 calculations⁷⁶ were performed for various bicyclo[5.3.1]undec-1(10)-enes together with their saturated counterparts.⁷⁷ These calculations suggested that the taxane bridgehead olefin system was remarkably unstrained, and possessed a smaller amount of strain energy than that of their saturated counterparts. Also modeled was the difference in

⁷⁶ Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

⁷⁷ Swindell, C. S.; Isaacs, T. F.; Kanes, K. J. *Tetrahedron Lett.* **1985**, *26*, 289.

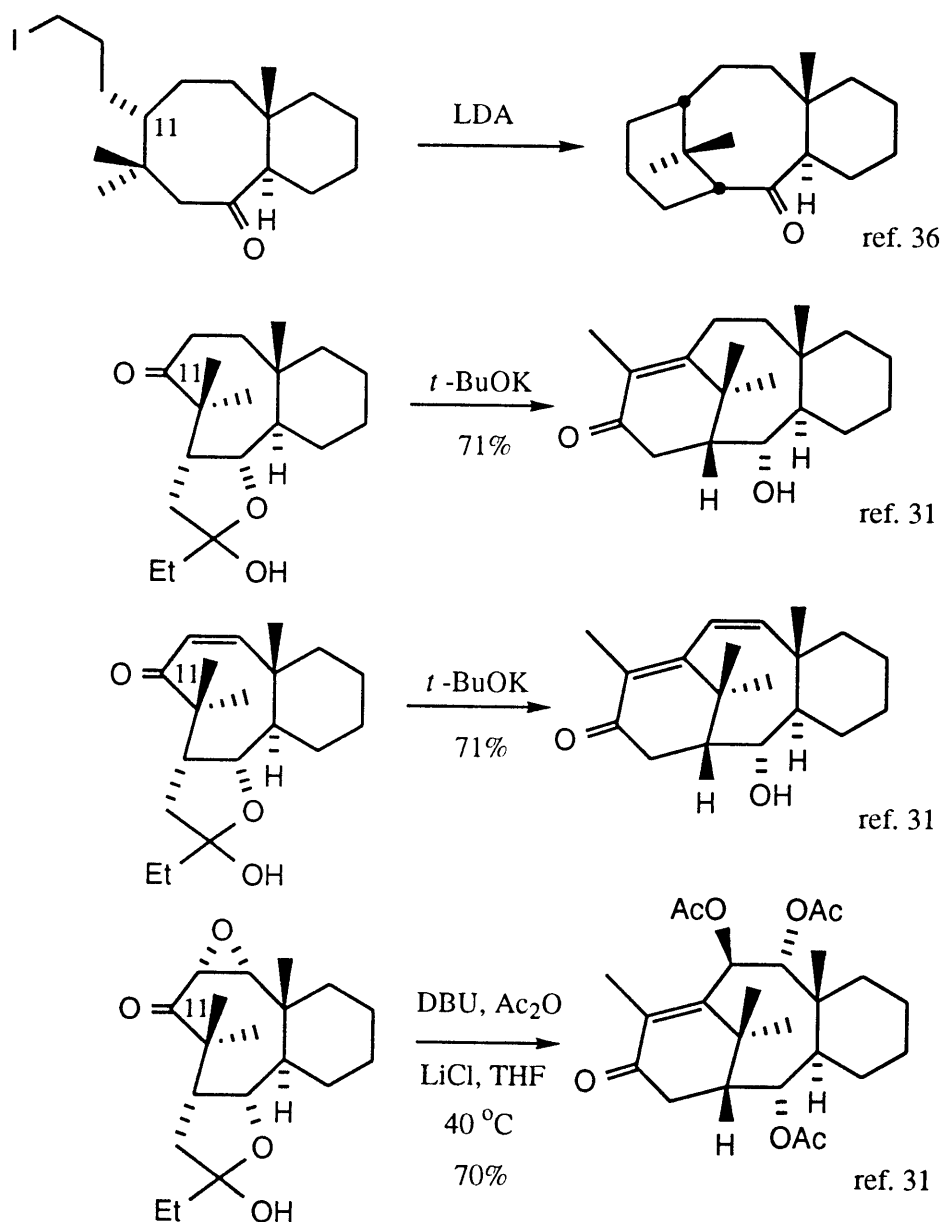
energy between the compound with an intact A-ring and its acyclic analog. His results (Scheme 46) showed that the energy required to close the A-ring was only 8.0 kcal/mol, as compared to 6.7 kcal/mol for *n*-pentane being converted to cyclopentane, 7.3 kcal/mol for *n*-heptane being converted to cycloheptane, and 10.7 kcal/mol for the conversion of *n*-octane to cyclooctane.



Scheme 46: MM2 calculations for taxane structures.

As a result of this study Swindell incorporated the A-ring annulation strategy into his synthetic plan, and successfully performed the ring closure on four systems (Scheme 47). The first system that was successful was an intramolecular alkylation via an enolate displacement of the side chain iodide.^{16a} Although this reaction did set the correct C(1) stereochemistry, the bridgehead olefin functionality was not constructed. The final three closures were more applicable to our system. All three possessed a cyclic hemiketal that was opened to form the side chain ethyl ketone upon exposure to basic conditions. This

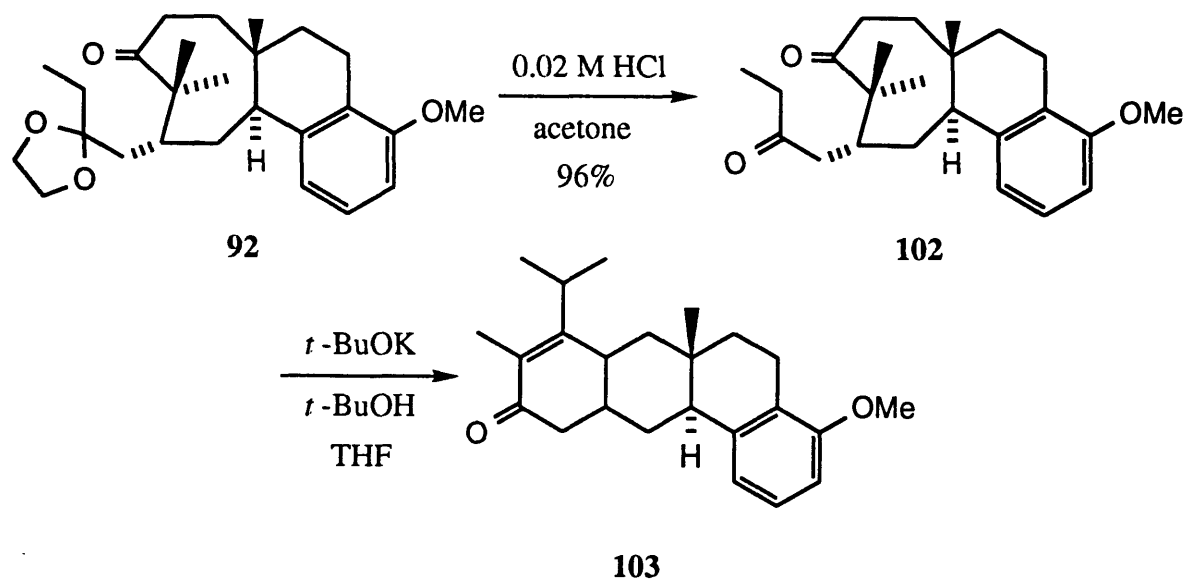
ethyl ketone cyclized, through an aldol closure, onto the C(11) ketone to form the A-ring. The final closure was not only the most useful toward the synthesis of taxusin, but it was also the most elegant. This was the tandem-aldol Payne rearrangement that resulted in the closure of the A-ring, and incorporated the C(9) and C(10) acetate groups in the correct stereochemistry.



Scheme 47: Previously performed A-ring annulations.

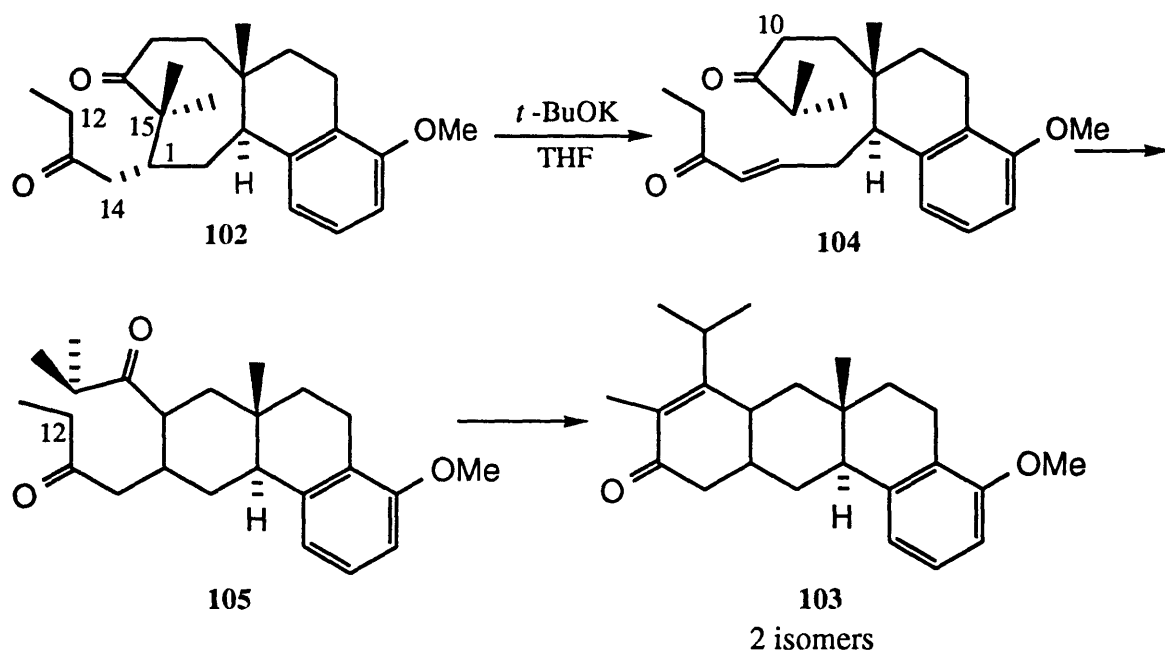
From this previous work that was performed on systems very similar to ours, it was expected that the A-ring annulation should be a reliable strategy, and efforts to proceed with the total synthesis of taxusin were undertaken. The first annulation that was attempted was on the unsubstituted B-C system, cyclooctanone **92**.

Towards this goal, the ketal was removed from cyclooctanone **92** via a transketalization reaction with acetone and hydrochloric acid to afford diketone **102** in 96% yield (Scheme 48). The cyclization was then attempted, by adding to a solution of diketone **102** in *tert*-butyl alcohol, excess potassium *tert*-butoxide. The reaction was quenched after 2 hours, and two stereoisomeric products were isolated, via flash column chromatography, as an inseparable mixture. Based on ^1H NMR analysis, both products possessed an isopropyl group which gave strong evidence for the cleavage of the cyclooctanone ring, resulting in the formation of tetracycle **103**.



Scheme 48: Attempted A-ring cyclization.

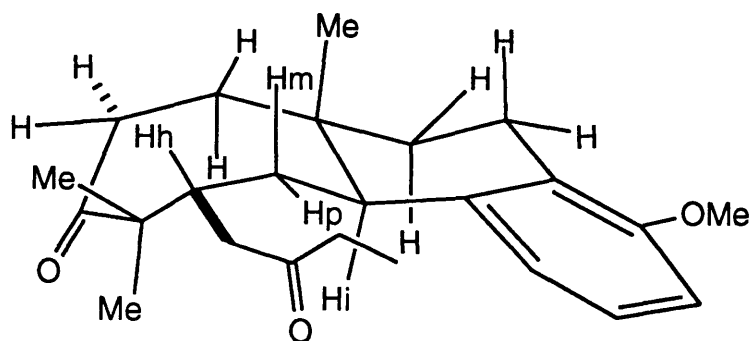
A possible mechanism for the reaction, shown in Scheme 49, results from the formation of an enolate of diketone **102** through deprotonation of the C(14) position instead of the desired C(12) position. When C(14) is deprotonated, a retro-Michael reaction can occur, breaking the bond between C(1) and C(15), resulting in the formation of enone **104**. Another enolate can then be formed from enone **104**, through deprotonation of the C(10) position, and a 1,4-addition to the enone can occur to form diketone **105**. One final enolate is then formed through deprotonation of C(12), and an aldol condensation results in the formation of tetracycle **103**.



Scheme 49: Possible mechanism for attempted A-ring cyclization.

Retro-Michael product **103** was unexpected, since, as previously stated, Swindell^{16a} had reported the successful A-ring cyclization of a very similar compound, with no reported evidence of the retro-Michael reaction having occurred. Consequently, rationalization for why our A-ring annulation attempt was unsuccessful suggested two possibilities: (1) we were erroneous in our analysis of the stereochemical outcome of the

cyclobutane fragmentation reaction leading to the *trans* -fused system **92**, or (2) our system was conformationally different in a way that favored the retro-Michael reaction. An examination of the preferred conformation of cyclooctanone **102** suggested reasons for why a reaction with base would result in a retro-Michael reaction. The preferred conformation, which was similar to that of cyclooctanone **79**, could be deduced through an analysis of the dihedral angles between the protons at the C(1), C(2), and C(3) positions (Scheme 50).



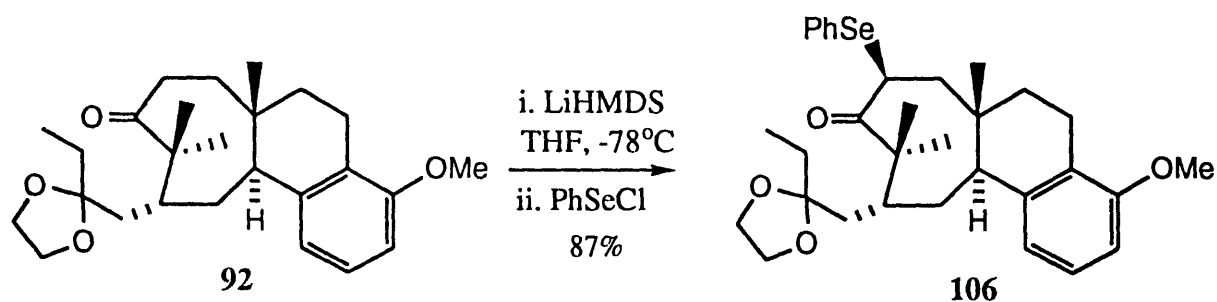
coupled partners	coupling constants
H _i H _m	12.9 Hz
H _i H _p	3.4 Hz
H _p H _h	12.3 Hz
H _m H _h	4.5 Hz

Scheme 50: ¹H NMR analysis of diketone **102**.

The proton at the C(3) position (H_i) was nearly 180° from the proton at the C(2β) position (H_m), which could be concluded from the large, 12.9 Hz, coupling constant, while H_i was only approximately 60° from the proton at the C(2α) position (H_p), as seen in the small, 3.4 Hz, coupling constant. Likewise, H_p was nearly 180° from the methine proton at the

C(1) position (H_h), as deduced from the large, 12.3 Hz, coupling constant while H_m was only approximately 60° from the H_h proton, which was concluded from the small, 4.5 Hz, coupling constant. Placing these protons in the correct conformation caused the ketone side chain to be in the pseudo-equatorial position shown in Scheme 50, where the C(14)-C(1) bond and the C(15)-C(11) bond were anti-periplanar to one another. Although, the overlap of the π -systems of the enolate, the C(15)-C(1) bond, and the C(11) ketone was not in perfect alignment for the fragmentation to occur, the system was thought to be conformationally stable enough to achieve the necessary overlap.

Although the result of the retro-Michael fragmentation was surprising and unfortunate, it could be rationalized, and from the conformational analysis above, it was assumed that the stereochemistry at the B-C ring juncture in cyclooctanone **92** was, in fact, correct. Consequently, the synthetic sequence toward the tandem-aldol Payne rearrangement was continued. Towards this goal, α -phenylselenenylketone **106** was formed from cyclooctanone **92** with lithium bis(trimethylsilyl)amide and phenylselenium chloride (see Scheme 51). These reagents were used in this case, because it was found that lithium diisopropylamide and phenylselenium bromide resulted in low yields.



Scheme 51: Formation of α -phenylselenenylketone **106**.

White cubes of α -phenylselenenylketone **106** were grown from a chloroform / hexane bilayer at 4°C to a size and quality suitable for X-ray diffraction. A total of 5704

reflections were collected at room temperature from a single crystal of **106** (0.380 mm x 0.350 mm x 0.350 mm) belonging to the $P2_12_12_1$ space group with the unit cell dimensions $a = 9.618(1) \text{ \AA}$, $b = 10.667(2) \text{ \AA}$, $c = 27.538(2) \text{ \AA}$, $Z = 4$. Least squares refinement of the data using 2930 reflections converged upon the structure of **106** as shown in Figure 3 with $R = 0.062$ and a goodness-of-fit = 1.22.⁷⁸ As revealed in Figure 3, the *trans*-stereochemistry at the B-C ring juncture is evident, as is seen at the randomly numbered (taxane numbering is not used) C(1)-C(9) bond. Also evident is the correct stereochemistry at the C(1) ketal side chain (randomly numbered in the X-ray structure as C(24)). Finally, from the X-ray structure, it is learned that the stereochemistry of the phenylselenium group is β as depicted in Scheme 48.

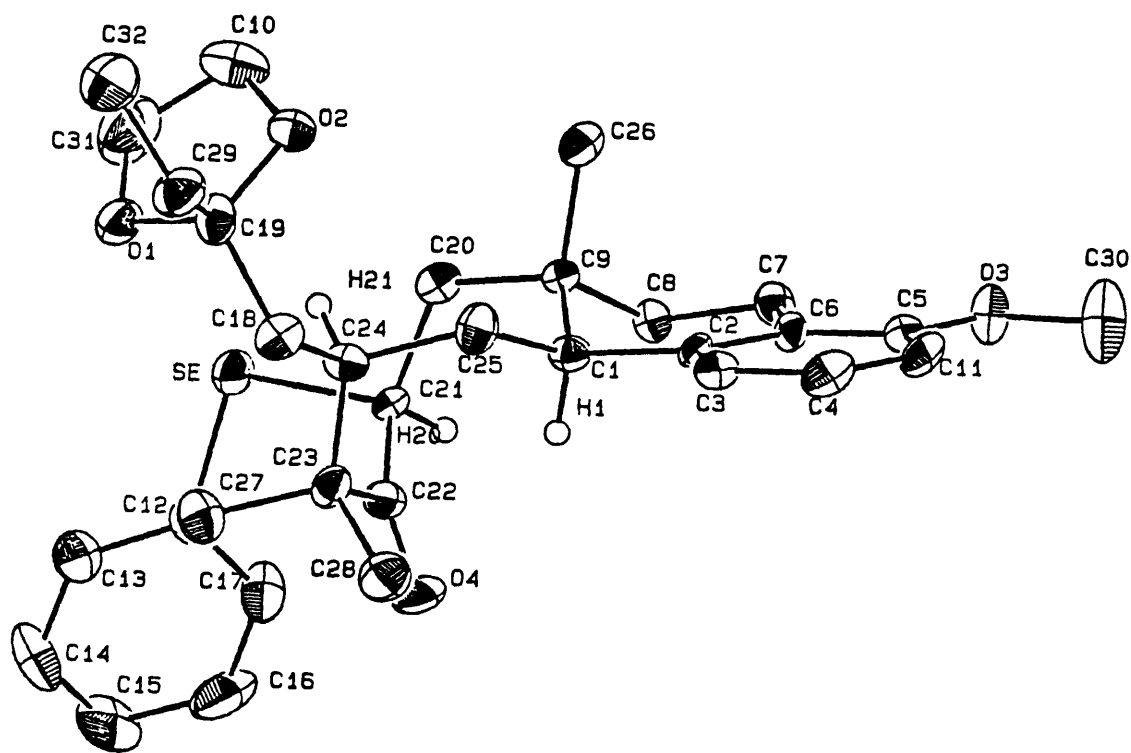
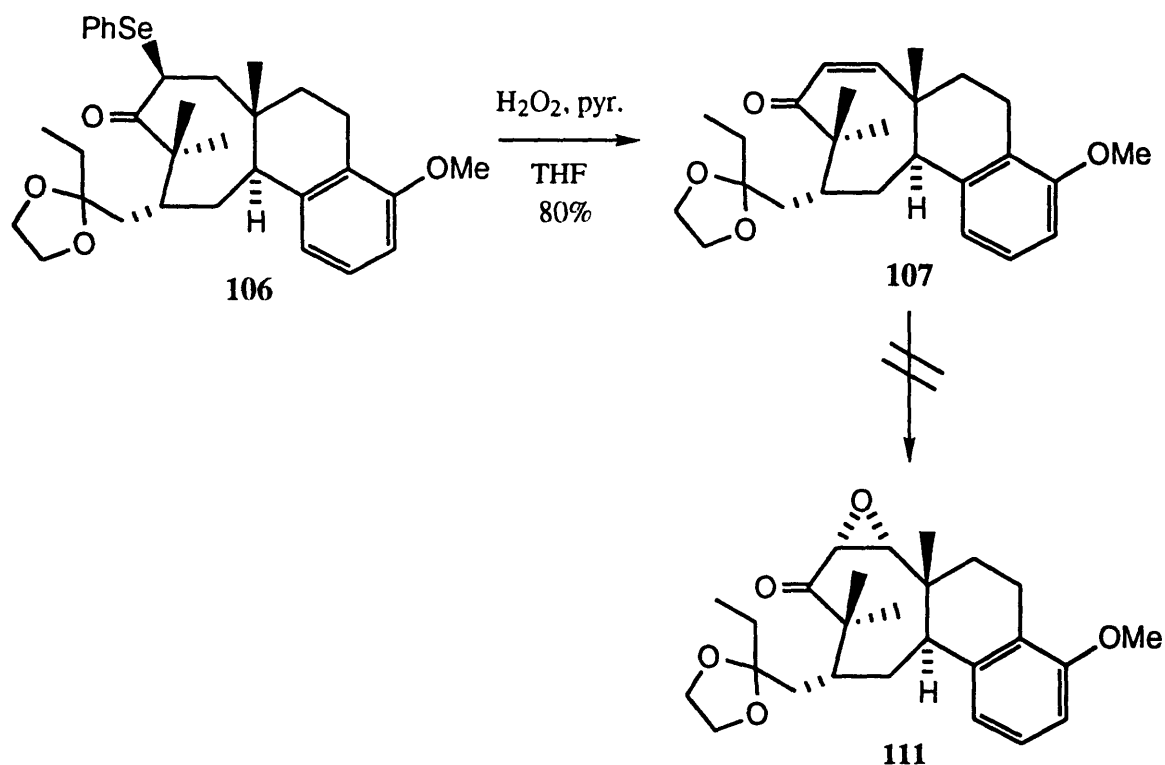


Figure 3: X-ray Structure of α -Phenylselenenylketone **106**

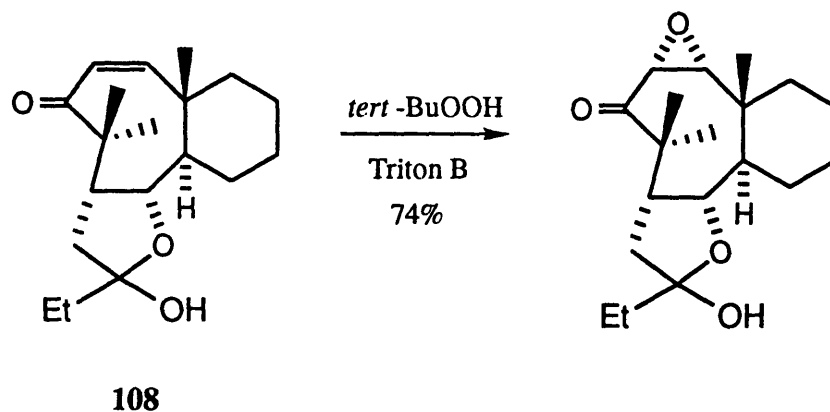
⁷⁸ The full details of the experimental procedure that was employed for the X-ray analysis of compound **106** as well as crystallographic data and atomic coordinates are the subject of work carried out by Dr. William Davis.

α -Phenylselenenylketone **106** was then smoothly eliminated by an oxidation to form the corresponding selenoxide with hydrogen peroxide in tetrahydrofuran and pyridine, which readily eliminated at room temperature to form enone **107** (Scheme 52). Attempts to cause the epoxidation of enone **107**, both nucleophilically via *tert*-butyl hydrogen peroxide and Triton B, sodium methoxide and hydrogen peroxide, and *tert*-butyl hydrogen peroxide and potassium *tert*-butoxide, and electrophilically using dimethyl dioxirane, *m*-chloroperoxybenzoic acid, and 3,5-dinitroperoxybenzoic acid were unsuccessful, resulting in the total re-isolation of starting material.



Scheme 52: Enone formation and attempted epoxidation.

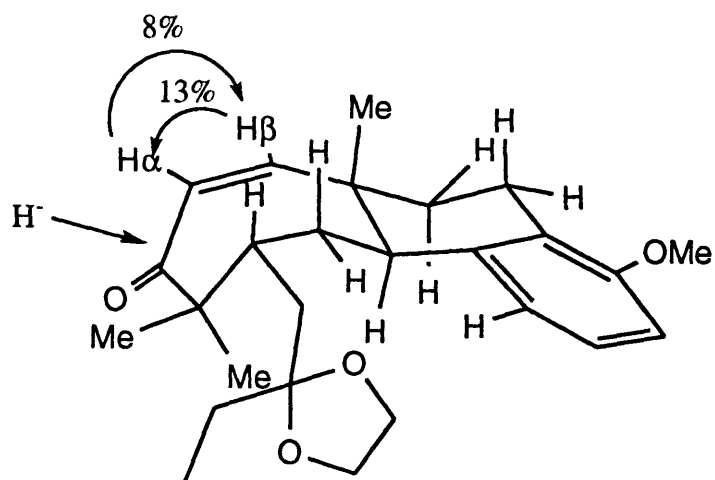
Failure of epoxidation attempts of enone **107** were also very unexpected, as Swindell successfully performed a nucleophilic epoxidation of a structurally similar compound, enone **108** (see Scheme 53), in his studies towards taxane synthesis.³¹ It was



Scheme 53: Swindell's enone epoxidation.

conjectured that, because of the medium-sized, eight membered ring, our elimination of α -phenylselenenylketone **106** could have resulted in the formation of a *trans*-double bond instead of the expected *cis* compound, and thus had caused the lack of success of the epoxidation of enone **107**. The fact that enone **107**, upon analysis via thin layer chromatography, was only weakly UV active when irradiated with an ultraviolet light source, as opposed to most strongly active enones, gave credence to this hypothesis. Therefore, in order to determine the stereochemistry of the double bond in enone **107**, nOe difference studies were performed (Scheme 54). When the olefinic proton β to the carbonyl was irradiated, a very strong 13% nOe was seen to the α -olefinic proton. Conversely, when the α olefinic bond was irradiated, an 8% nOe was seen to the β -olefinic proton. Through this analysis, the desired *cis*-stereochemistry of the olefin bond was proven.

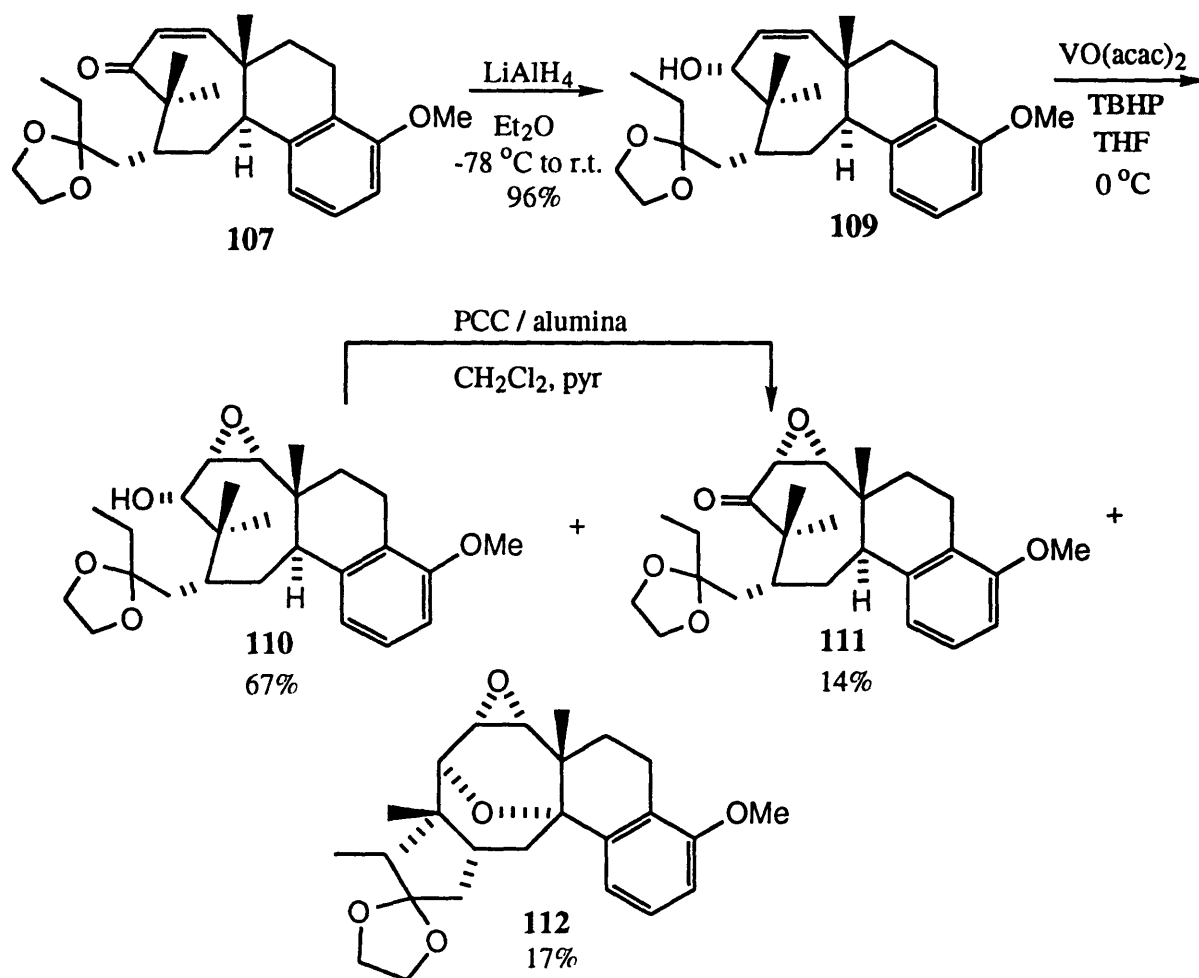
The failure of the epoxidation of enone **107** created the necessity to obtain epoxy ketone **111** through a less direct route. Consequently, enone **107** was reduced to allylic alcohol **109** with lithium aluminum hydride. It was assumed from the X-ray structure of α -phenylselenenylketone **106**, which showed the ketone existing in a conformation folding



Scheme 54: nOe difference studies and expected hydride approach to enone **107**.

down, away from the phenylselenide group, that a hydride source would approach the ketone from the convex side of the molecule (Scheme 54), therefore creating the α -stereochemistry apparent in allylic alcohol **109** (Scheme 55). From this analysis, epoxidation with vanadyl acetylacetonate and *tert*-butyl hydroperoxide was expected to afford the desired epoxide stereochemistry, shown in epoxy ketone **111**, through an epoxidation on the same face as the alcohol functional group.⁷⁹ Performance of the epoxidation resulted in the formation of three products -- epoxy alcohol **110** in 67% yield, epoxy ketone **111** in 14% yield, and cyclic ether **112** in 17% yield, which was an interesting compound, because numerous efforts in our laboratory to oxidize the C(3) benzylic position towards the synthesis of taxol were unsuccessful. Epoxy alcohol **110** was converted to epoxy ketone **111** through an oxidation with pyridinium chlorochromate on neutral alumina in 87% yield. Therefore, including the 14% epoxy ketone **111** obtained from the epoxidation with vanadyl acetylacetonate, epoxy ketone **111** was formed from enone **107** in three steps in a 69% overall yield as a single stereoisomer.

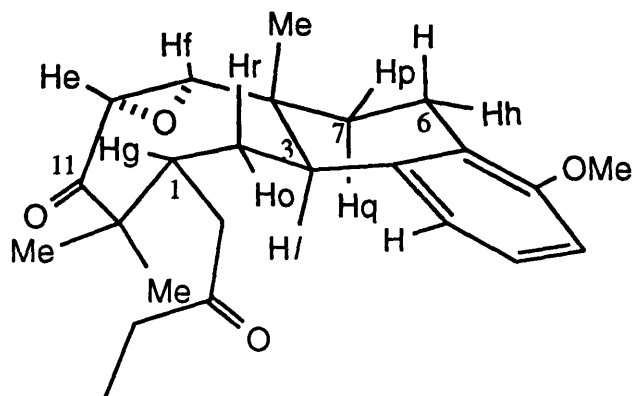
⁷⁹ Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.



Scheme 55: Conversion of enone **107** to epoxy ketone **111**.

The ketal protecting group of epoxy ketone **111** was then removed through a transketalization reaction with acetone and hydrochloric acid in 97% yield (see Scheme 56), and nOe difference studies were performed on the resulting epoxy diketone **113** to not only ascertain the stereochemistry of the epoxide group, but to also prove that the epoxide existed in the correct regiochemistry. When the protons at the C(7) position were irradiated (they were irradiated at together due to their proximity in the NMR), a 4% nOe was seen to epoxide proton H_f, a 5% nOe was seen to the C(6α) proton, H_h, and a 4% nOe was seen to the proton at the C(3) ring juncture, H_l. These observations proved, unequivocally, that

the desired regiochemistry of the epoxide was present. To prove the stereochemistry of the epoxide, the C(1) methine proton, H_g, was irradiated which showed a 5% nOe to epoxide proton, H_e. This result definitively proved that the epoxide was the desired diastereomer.

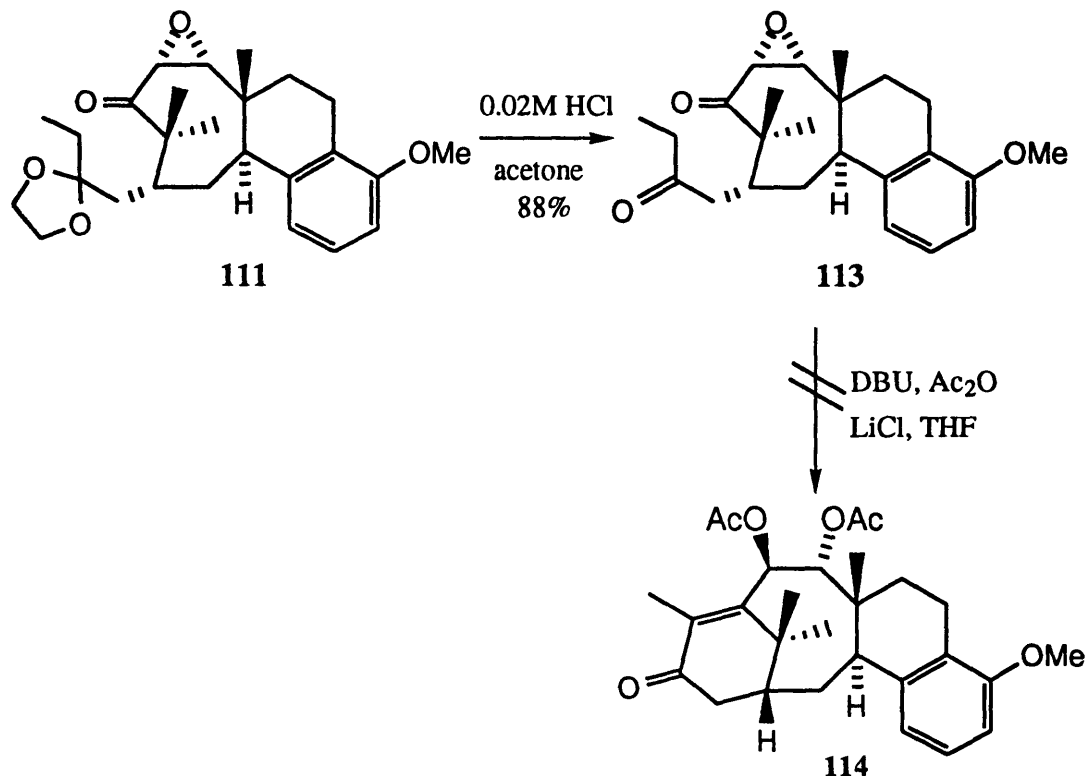


<u>Irradiated ppm</u>	<u>Observed nOe</u>
1.74 ppm (H _p & H _q)	H _f (4%) H _h (5%) H _i (4%)
3.10 ppm (H _g)	H _e (5%)

Scheme 56: Analysis of nOe difference spectra of epoxy diketone **113**.

At this point, the tandem-aldol Payne rearrangement was performed (Scheme 57). According to Swindell's procedure, epoxy diketone **113** (3 mg, 0.008 mmol) was dissolved in 80 μ L tetrahydrofuran that was saturated with lithium chloride. To this solution was added 0.12 mmol diazabicycloundecane (DBU), and 0.12 mmol acetic anhydride. The reaction was warmed to 40 $^{\circ}$ C, at which temperature, the procedure stated that reaction went to completion in 15 minutes. When no reaction occurred after one hour, the reaction was heated to 90 $^{\circ}$ C (bath temperature) for one hour. At this time the reaction was worked up, and NMR analysis revealed that the only isolated compound was,

unfortunately, starting material. The reaction was repeated, and the reaction mixture was stirred at 40 °C for 24 h. Upon workup, a single compound was again isolated, and NMR analysis proved it to again be starting material.



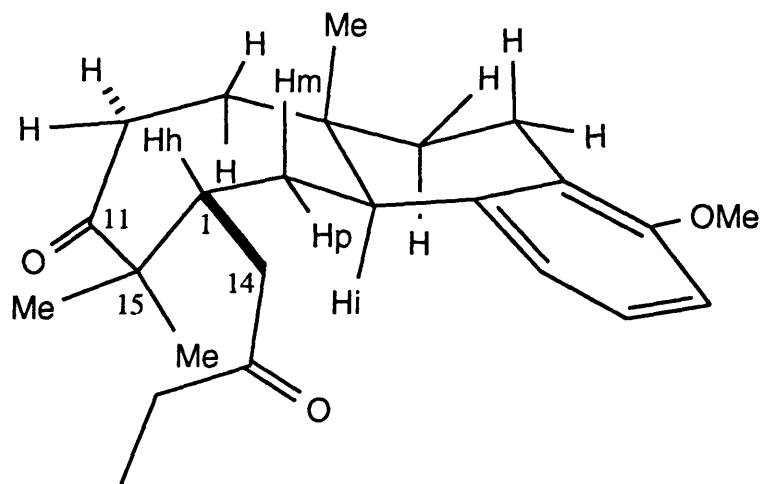
Scheme 57: Attempted tandem-aldol Payne rearrangement.

This was a serious synthetic setback, as it was hoped the tandem-aldol Payne rearrangement would not only cause the annulation of the A-ring, but it would also set the stereochemistry of the C(9) and C(10) acetate groups to form compound **114**. Analysis of the preferred conformation of the epoxy ketone suggested that it existed in the same conformation as that in cyclooctanone **102**, with the ketone side chain dangling out to the side of the molecule as is represented in Scheme 50. This could create a considerable energetic barrier for the side chain to swing around "underneath" the molecule where it would be in a position to react with the C(11) ketone. However, the fact that starting

material was isolated suggested that the enolate was not being formed. This is because one would expect that the formation of an enolate would result in the creation of the corresponding enol acetate if no cyclization was occurring.

4.2 Alternative Strategies

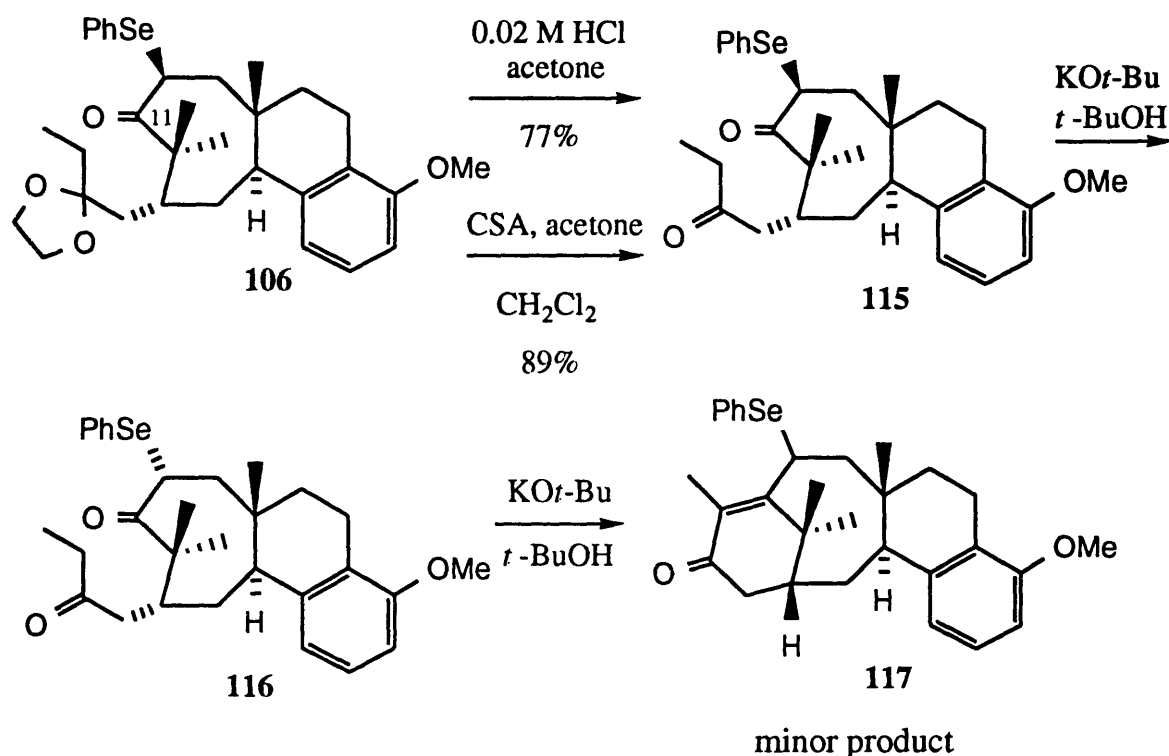
The failure of the tandem-aldol Payne rearrangement created a need for an alternative synthetic plan for the closure of the A-ring. Toward this end, various systems were constructed upon which the A-ring annulation was attempted. The first of these systems that was fabricated tested the hypothesis that substitution α to the C(11) ketone could alter the conformation of the system in a manner that would disfavor the retro-Michael reaction by forcing the C(14)-C(1) and C(15)-C(11) bonds out of their antiperiplanar alignment. This was also hoped to cause the cyclization to be energetically favorable (Scheme 58).



Scheme 58: Antiperiplanar alignment of the C(14)-C(1) and C(15)-C(11) bonds.

α -Phenylselenenylketone **106** was deemed an appropriate compound to test this hypothesis, because it was not only readily available, but it also could be useful toward creating a fully-functionalized B-ring in taxusin through the eliminated dienone (Scheme 59). Deprotection of the ethylene ketal, however, was problematic. Transketalization conditions with hydrochloric acid and acetone proved to be too harsh, as removal of the

phenylselenide group was inevitable -- even with dilute acid solutions of 0.006M, 23% of the phenylselenide group was removed. Deprotection was accomplished with an acetone solution of camphorsulfonic acid, which presumably acted as a "bulky" acid, and therefore would not easily protonate the neopentyl C(11) ketone; therefore, an 89% yield of α -phenylselenenyldiketone **115** was isolated.

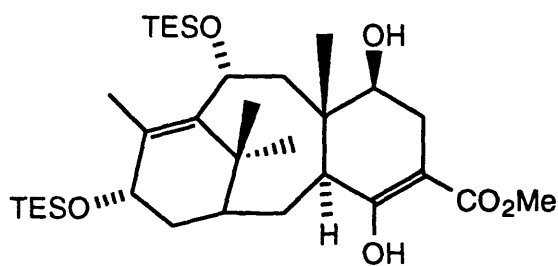


Scheme 59: Annulation of α -phenylselenenyl ketone **106**.

Annulation of the A-ring on α -phenylselenenyldiketone **115** was attempted with potassium *tert*-butoxide in a solution of *tert*-butanol (Scheme 59). The reaction was stirred at room temperature for 2 h at which time all of the starting material had disappeared as evidenced by analysis via thin-layer chromatography. After workup, ^1H NMR analysis revealed that the only product was α -phenylselenenyldiketone **116** where epimerization of the selenide group had occurred. α -Phenylselenenyldiketone **116** was resubmitted to the previous reaction conditions of potassium *tert*-butoxide in *tert*-butyl alcohol. After the

reaction had been stirred at room temperature overnight, analysis of the reaction mixture via thin-layer chromatography revealed a complex mixture of products. The reaction mixture was viewed via a crude ^1H NMR which showed that the selenide group had been removed for much of the mixture; however, a minor product appeared to be the desired tricyclic compound **117**. This was evidenced by the presence of a triplet that was 1 ppm downfield from the original doublet of doublets for the proton α to the selenide group along with peaks in the aromatic region that corresponded to the phenylselenium protons. Since the triplet possessed the expected chemical shift and multiplicity for proton α to the selenide group ($\text{H}\alpha$ in Scheme 59) which was now in conjugation with the enone and confined in a rigid tricyclic system, the desired tricyclic compound **117** was thought to have been formed in a small amount. There were no compounds where the occurrence of the retro-Michael cleavage of the B-ring was apparent.

Because of the formation of several products in the above reaction, the ease of the removal of the selenide group, and the desired compound being formed as a very minor product that decomposed upon isolation, it was surmised that the usage of α -phenylselenenylketone **106** as a vehicle for the successful annulation of the A-ring would not be prudent. However, the observations that the retro-Michael reaction did not occur on this compound, and that some of the desired product, even in a very small amount, was possibly formed, created reasons to believe that substitution α to the C(11) ketone could, in fact, enable the successful annulation of the A-ring. Therefore, another system was designed utilizing an α -substituted intermediate (Scheme 60). In his synthesis of taxol,²⁵



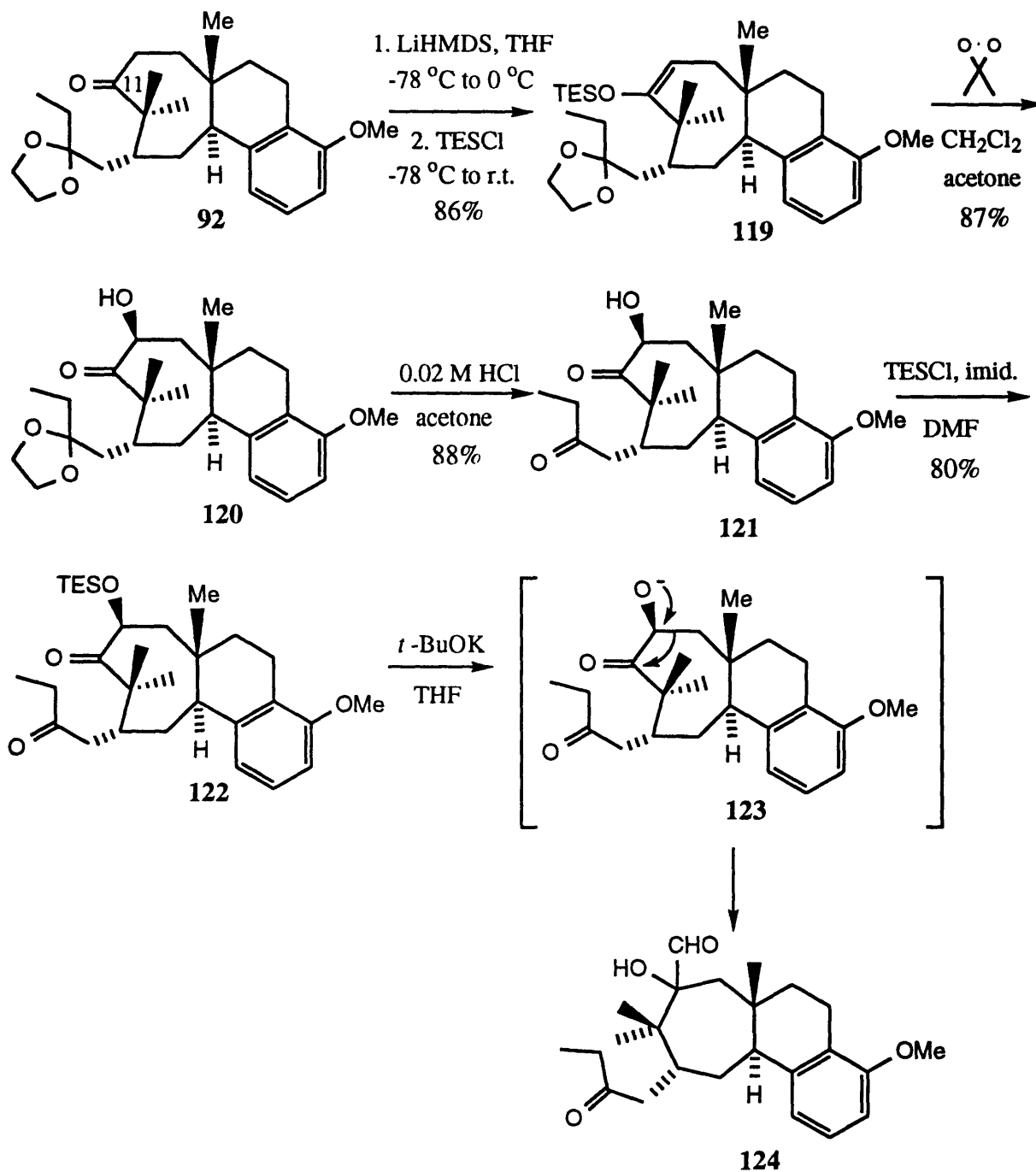
118

Holton used C(10)-triethylsiloxy-substituted compound **118** as a key intermediate through which, the total functionalization of the B-ring was accomplished. Therefore, the second α -substituted system that was designed in our synthetic efforts incorporated the C(10)-triethylsiloxy functionality (Scheme 60).

C(10)-Triethylsiloxy diketone **122** was successfully synthesized from cyclooctanone **92** by first forming triethylsilyl enol ether **119**. Deprotonation was accomplished with lithium bis(trimethylsilyl)amide in a solution of tetrahydrofuran at -78°C followed by warming to 0°C . Chlorotriethylsilane was then added at -78°C , and the reaction was warmed to ambient temperature to form triethylsilyl enol ether **119** in 86% yield. Epoxidation of triethylsilyl enol ether **119** was performed with dimethyl dioxirane⁸⁰ in an acetone solution⁸¹, during which the triethylsilyl group was unexpectedly removed to afford α -hydroxy ketone **120** in 87% yield. At this point, removal of the ketal protecting group was deemed appropriate, due to the possibility of another cleavage of the triethylsilyl group under deketalization conditions. Therefore, 10-hydroxy-11,13-diketone **121** was formed in 88% yield through removal of the ethylene ketal with 0.02 M hydrochloric acid in acetone. The final step prior to the attempted A-ring annulation was the formation of 10-triethylsiloxy-11,13-diketone **122** from α -hydroxyketone **121** with chlorotriethylsilane and imidazole in *N,N*-dimethylformamide. This afforded α -siloxyketone **122** in four steps from cyclooctanone **92** in 53% overall yield.

⁸⁰ (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 305. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. "Advances in Oxygenated Processes"; Baumstark, A. L. (Ed.); Vol. 2, Chapter 1, JAI Press: Greenwich, 1990. (d) Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Siedel, B. *Tetrahedron Lett.* **1989**, *30*, 4223. (e) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249.

⁸¹ (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 1979. (b) Adam, W.; Chan, Y. -Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (c) Eaton, P. E.; Wicks, G. E. *J. Org. Chem.* **1988**, *53*, 5353.



Scheme 60: Synthesis and attempted annulation of α -triethylsiloxy analog.

The A-ring annulation was attempted with potassium *tert*-butoxide in a solution of tetrahydrofuran. Analysis of the reaction via thin-layer chromatography indicated that the

starting material was proceeding to one, slightly more polar, product which, in turn, was proceeding to another more polar compound. The first product was not isolated, as it was assumed to be the C(10) epimer as in the attempted annulation reaction of α -phenylselenyl ketone **115**. When both the starting material, and the presumed C(10) epimer had disappeared the reaction was worked up, and the major product was isolated via flash column chromatography. ^1H NMR analysis revealed that the major product of the reaction was cycloheptane **124**. This product was presumably formed first through the nucleophilic displacement of the silyl group to give alkoxide intermediate **123** which could have undergone ring contraction, breaking the C(9)-C(10) bond, to form hydroxy cycloheptanal **124**.

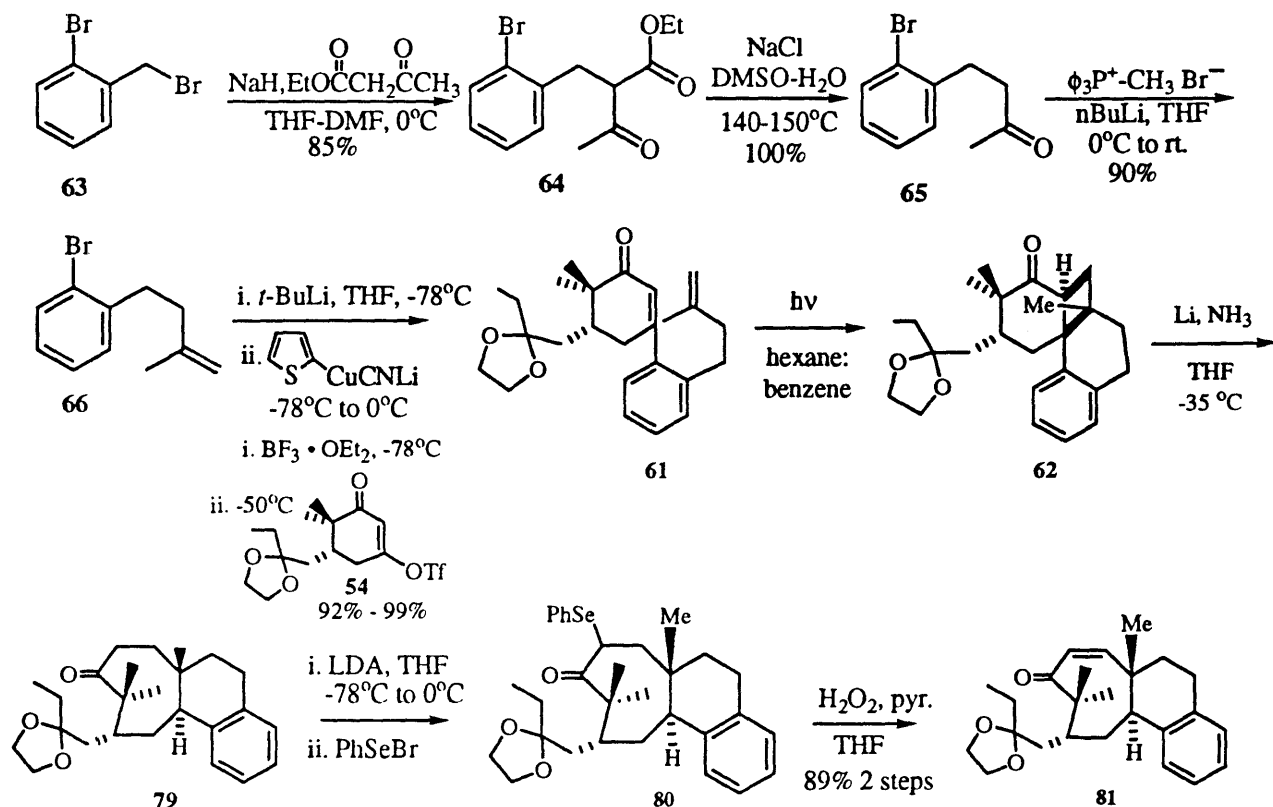
This result, while it was not entirely unforeseeable, was quite disappointing. The propensity of the *trans* -B-C ring system for fragmentation had been established in our earlier work, and it was known that triethylsiloxy groups could be cleaved with nucleophiles such as sodium methoxide;⁸² however, it was unexpected that the protecting group would be cleaved by a very bulky base such as *tert* -butoxide. It was also unexpected that none of the desired, ABC, tricyclic compound was isolated or observed.

At this point, a few ideas could be postulated that could cause the fragmentation to be disfavored. The main plan was to protect the α -hydroxy group with a less labile protecting group such as a *tert* -butyl(dimethyl)silyl group, which was expected to prevent the formation of the free alkoxide, and consequently prevent the fragmentation. However, just because the fragmentation would be blocked by a hearty protecting group, did not guarantee that the cyclization would work. It was still possible that the retro-Michael reaction would occur, resulting in a different fragmentation product. For these reasons, the focus of the project was shifted from attempting to cyclize the A-ring, to the removal of the aromatic ring.

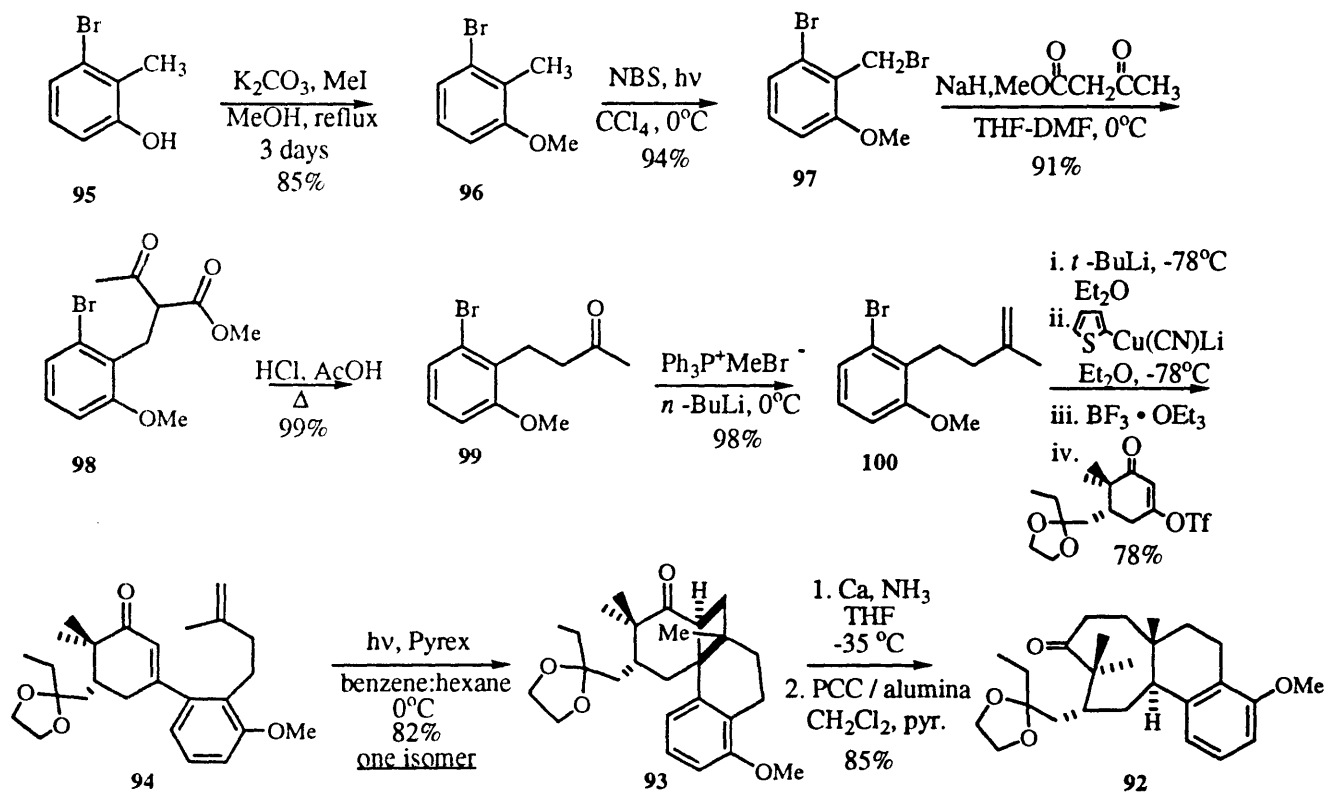
⁸² Greene, T. A.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 2nd. Ed. John Wiley and Sons, Inc. 1991, pg. 296.

4.3 Summary

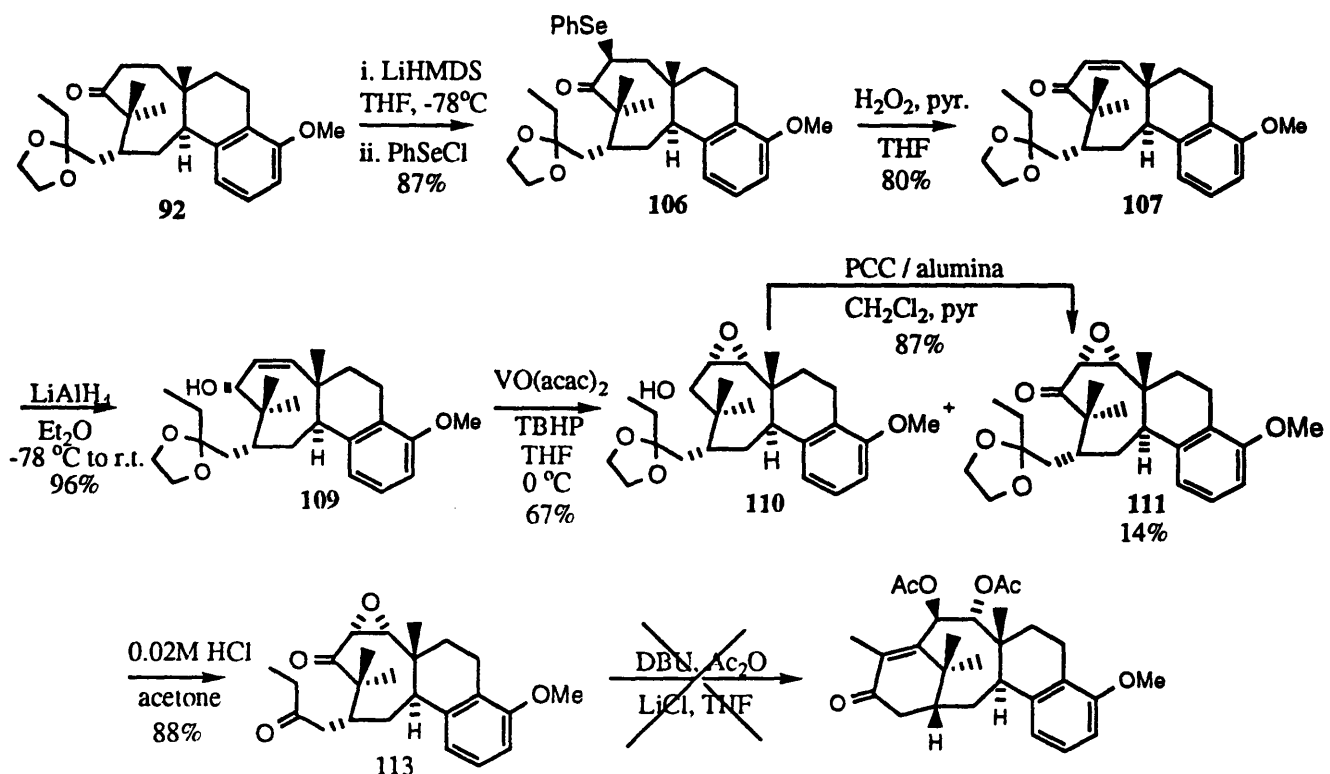
Model System Studies



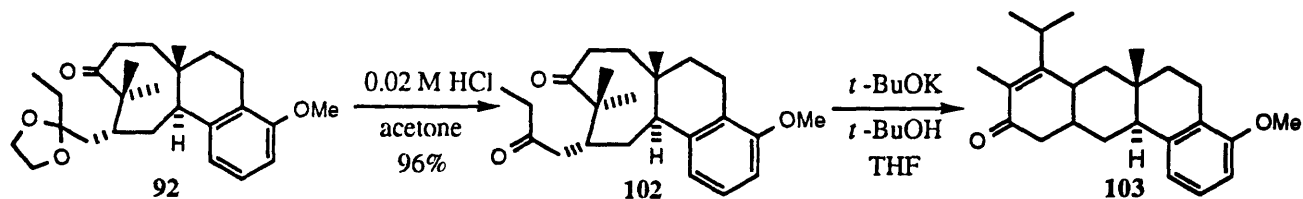
Methoxy Analogs



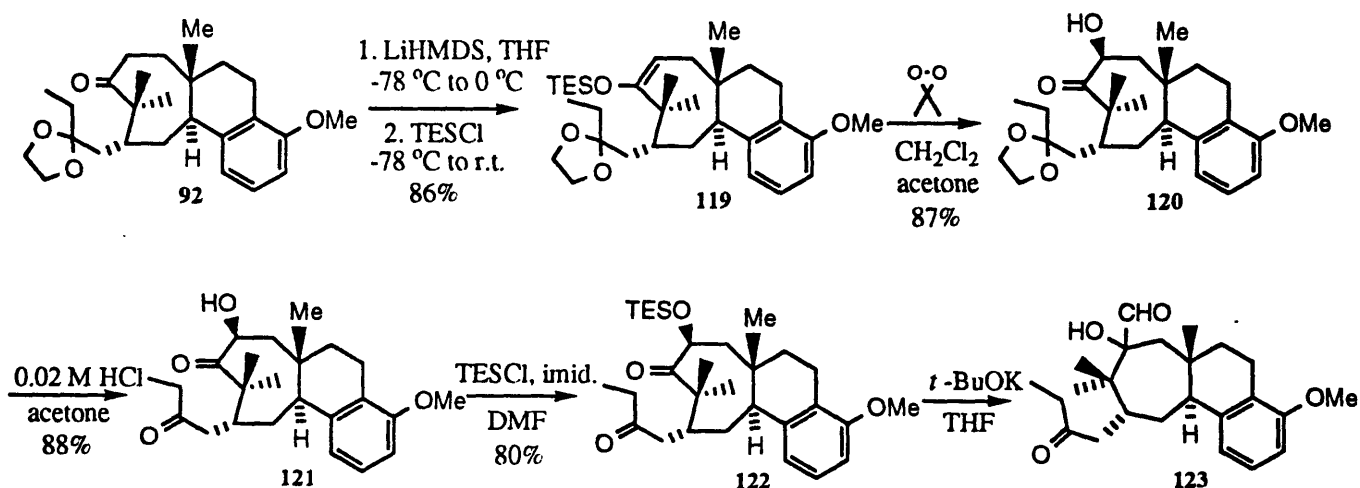
Efforts Toward the Tandem-aldol Payne Rearrangement



Retro-Michael Fragmentation



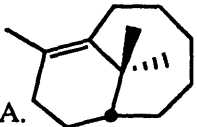
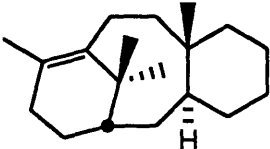
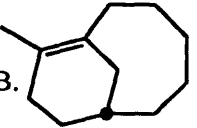
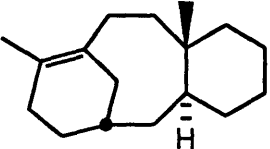
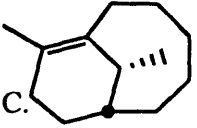
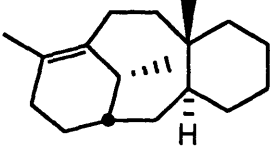
Cyclization of α -Triethylsiloxy Ketone



Chapter 5. Cleavage of the Aromatic Ring

5.1 Cleavage via Birch Reduction and Ozone Techniques

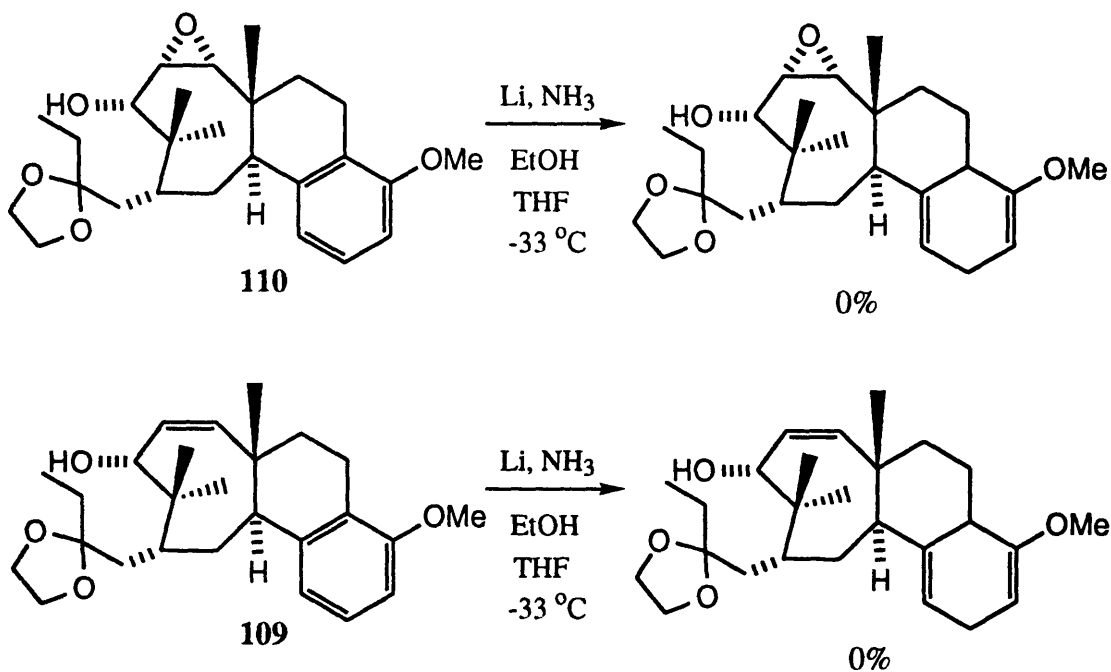
Because all attempts to create the taxane framework through an A-ring annulation of an aromatic-substituted intermediate were unsuccessful, it was hypothesized that the aromatic ring could be contributing to the failure of the reaction by either altering the electronics or the conformation of the system. Swindell, in his MM2 calculations on the taxane bridgehead olefin stability (previously discussed on page 70) had suggested that the C-ring conformation had an important effect on the stability of the A-ring bridgehead olefin (Scheme 61). In this study, taxane A-B systems were modeled, incorporating the bridgehead olefin functionality, and they were compared to the corresponding ABC system that also included the bridgehead olefin functionality. The result of these studies showed that the calculated strain energies for the tricyclic compounds were approximately 10

	ΔH°_f	Strain energy		ΔH°_f	Strain energy
A. 	-12.06	32.45		-27.11	42.21
B. 	-8.69	20.03		-23.40	30.14
C. 	-8.34	27.79		-24.76	36.18

Scheme 61: Swindell's MM2 calculations for taxane structures.

kcal/mol higher in energy than their corresponding bicyclic compound. Additionally, through the modeling of possible C-ring conformers of various tricyclic structures, he noted the stability of the bridgehead olefin was also dependent on the C-ring conformation. Consequently, these calculations suggested that differences in carbon hybridizations in the C-ring could effect the outcome of the A-ring annulation, and since Swindell, in his successful A-ring annulations, incorporated no functional groups onto the C-ring, it was postulated that the aromatic moiety in our system could be causing the failure of the A ring-closure.

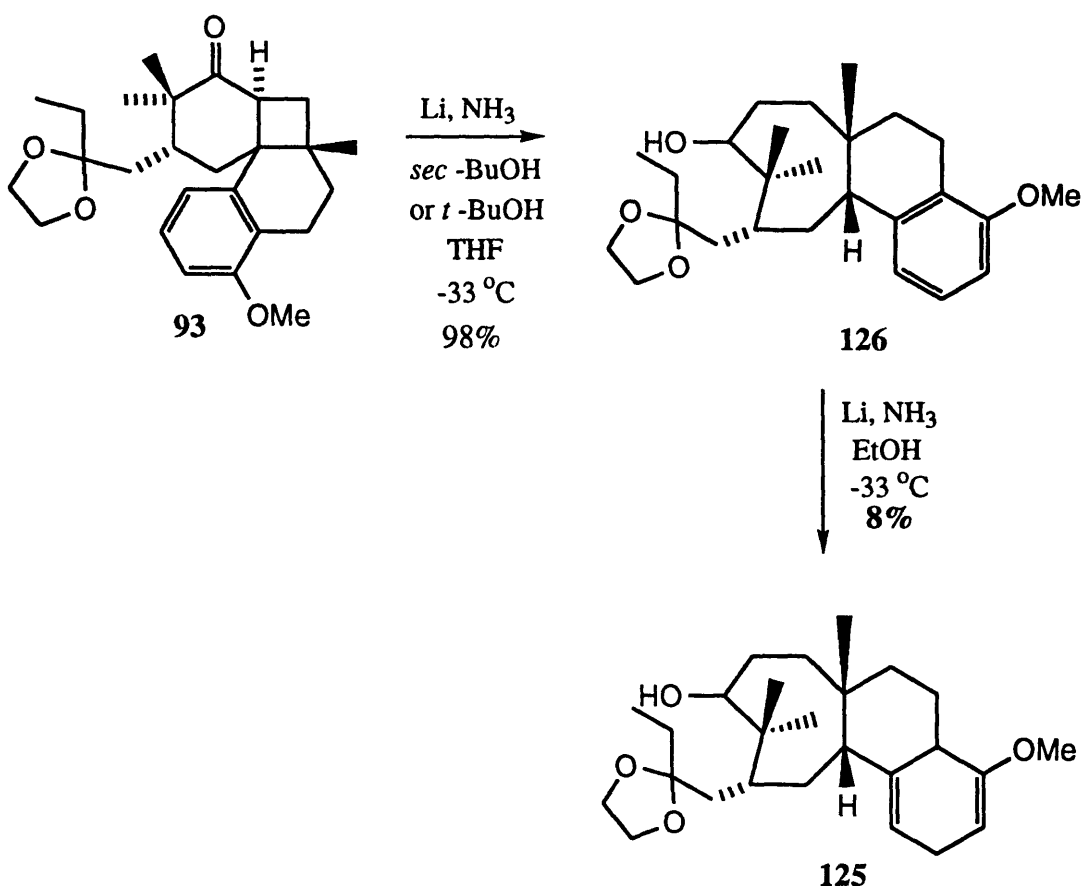
Therefore, at this point, efforts to cleave the aromatic ring via the previously described Birch reduction / ozonolysis sequence were undertaken. Initial efforts to reduce the aromatic ring were performed on highly substituted intermediates following the strategy that, if successful, the tandem-aldol Payne rearrangement could be attempted directly



Scheme 62: Initial Birch reduction attempts.

following the reduction. This would alleviate possible protecting group problems that might be encountered while functionalizing the B-ring in the presence of a fully functionalized C-ring. Therefore, the Birch reduction was first attempted on epoxy alcohol **110** and allylic alcohol **109** (Scheme 62). In the presence of lithium, liquid ammonia, and ethanol at -33 °C both compounds afforded a complex mixture of products; however, evident in the crude ¹H NMR spectra of both reactions was the fact that, although many functional group reactions had occurred, the aromatic portion of the molecules was still intact. No peaks corresponding to the desired diene were visible.

Cleavage of the aromatic ring was then attempted on a less functionalized intermediate. It was expected that ring opening of cyclobutane **93** and subsequent reduction of the aromatic ring could be performed in a one-pot conversion to afford diene **125** (Scheme 63); however, multiple attempts of this reaction, varying proton sources, temperatures, solvents, and order of addition, resulted in the formation of a single product -- alcohol **126** -- with no evident reduction of the aromatic ring. The best yield of diene **125** was obtained by performing the ring opening of cyclobutane **93** as a reaction separate from the aromatic ring reduction. This was achieved through the addition of a solution of cyclobutane **93** in tetrahydrofuran to excess lithium in liquid ammonia followed by the separate addition of *sec*-butyl alcohol (*tert*-butyl alcohol could also be used) to afford alcohol **126** in 98% yield. Alcohol **126** in a tetrahydrofuran solution was again added to excess lithium in liquid ammonia, and the reaction was stirred for 2 h. Ethanol was then added as the proton source and the reaction was stirred for an additional 2 h. After workup, a crude ¹H NMR revealed an 8% presence of the desired diene **125**.



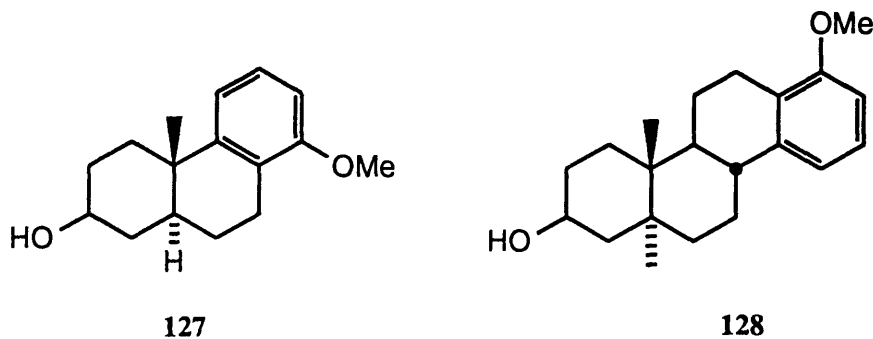
Scheme 63: Birch reduction.

These efforts toward the Birch reduction resulted in two observations: 1) the forcing conditions of this reaction afforded the *cis* -B-C ring juncture as opposed to the previously formed *trans* compound (this result is discussed in section 5.2, but the compounds are shown possessing the correct stereochemistry), and 2) the α -anisole compounds were very resistant to dissolving metal conditions. A close examination of the literature suggested reasons for the low yields that were obtained for the Birch reduction. Compounds **127**⁸³ and **128**⁸⁴ containing a similar 5-methoxytetralin moiety also manifested a resistance to dissolving metal reductions. This result suggested that the poor

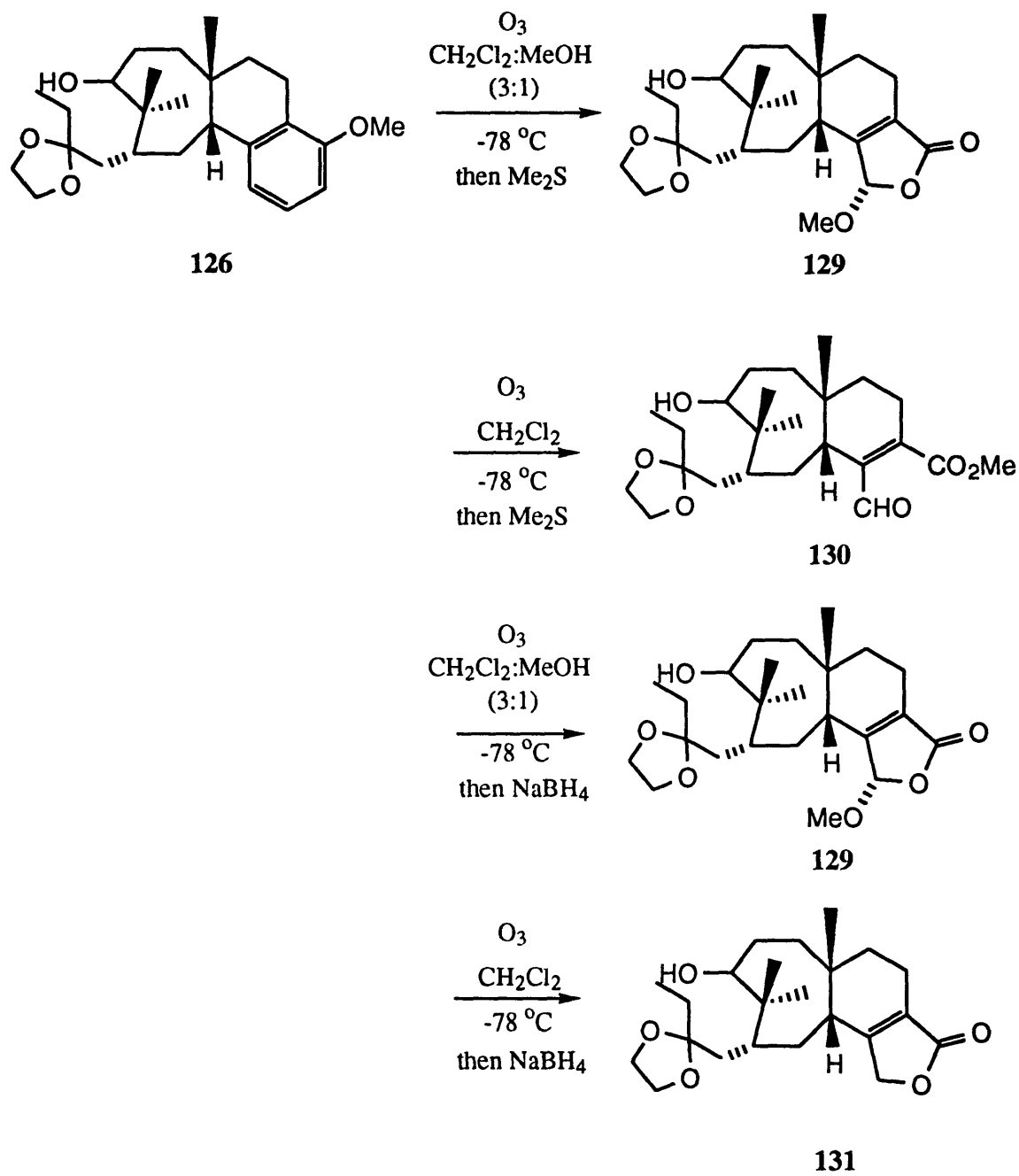
⁸³Johnson, W. S.; Bannister, B.; Rappo, R. *J. Am. Chem. Soc.* **1956**, *78*, 6331.

⁸⁴Turner, R. B.; Ganshirt, K. H.; Shaw, P. E.; Tauber, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1776.

reactivity of the α -anisole group was due to the fact that the normal course of the reduction required protonation to occur at a site bearing an alkyl substituent. Only in cases where intramolecular protonation could occur was the Birch reduction successful in reasonable yields.

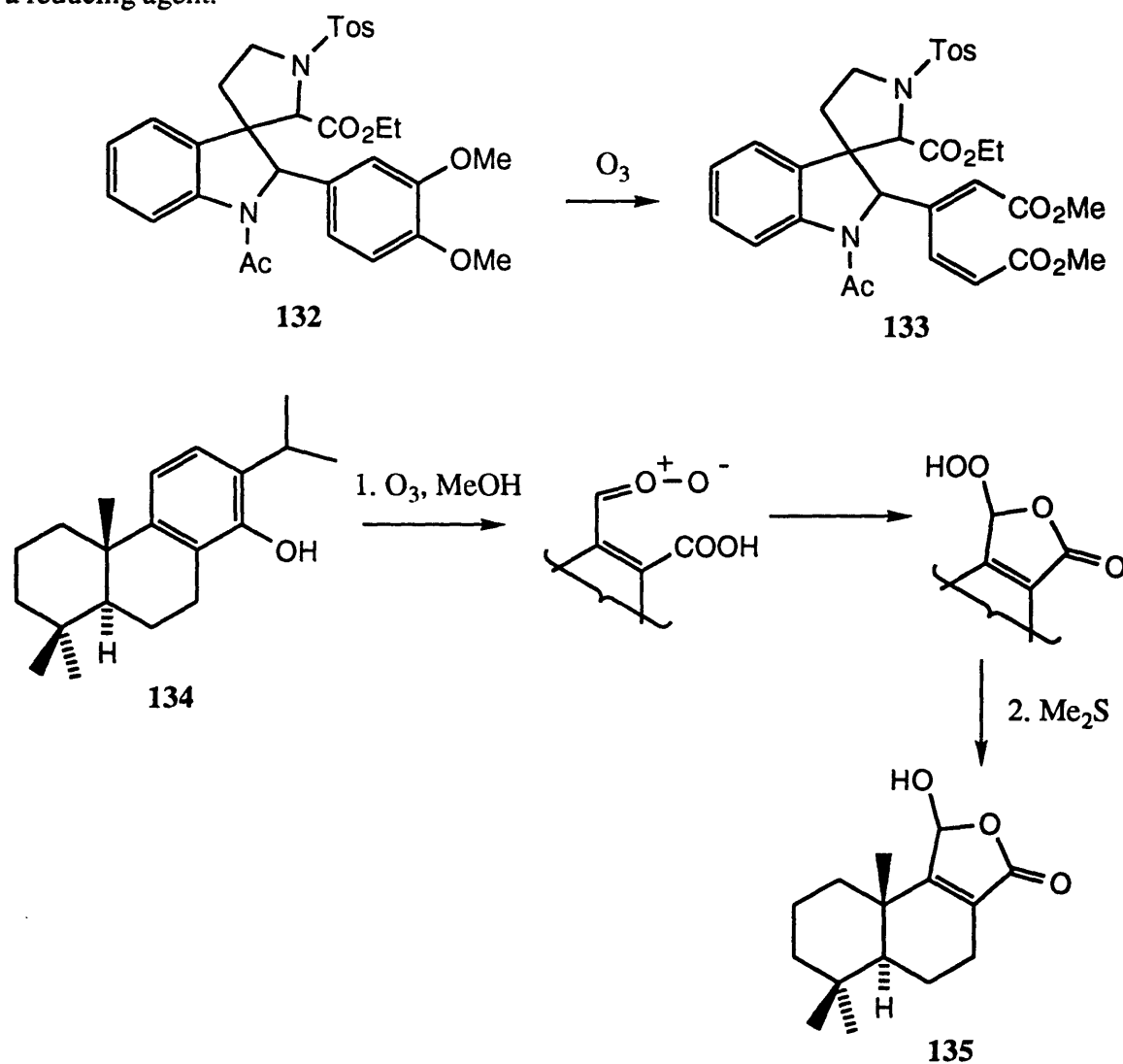


Although the Birch reduction of compound **126** resulted in low yields, the crude mixture containing the 8% yield of desired diene **125** was submitted to oxidation with ozone. During this reaction, not only was diene **125** cleaved to form an oxidized product, but alcohol **126** was also oxidized. This was envisioned to be a more useful reaction, due to the low yield leading to the formation of diene **125**. Alcohol **126** was then submitted to various reaction conditions leading to its ultimate ozonolysis. The results of this study (Scheme 64) were as follows: when alcohol **126** was subjected to ozone in a 3:1 mixture of dichloromethane and methanol at -78°C followed by the addition of dimethyl sulfide, acetal lactone **129** was formed in a 58% yield. In the absence of methanol, under identical reaction conditions, conjugated ester aldehyde **130** was isolated in a 60% yield. It was thought that the addition of sodium borohydride to the reaction conditions would result in the reduction of not only the ozonides, but also the resulting aldehyde to form either the hydroxy ester or the corresponding lactone. However, with the inclusion of methanol in the solvent mixture, acetal lactone **129** was still formed with no evidence of a reduced product. In the absence of methanol, sodium borohydride did cause the reduction of the aldehyde to form lactone **131**.



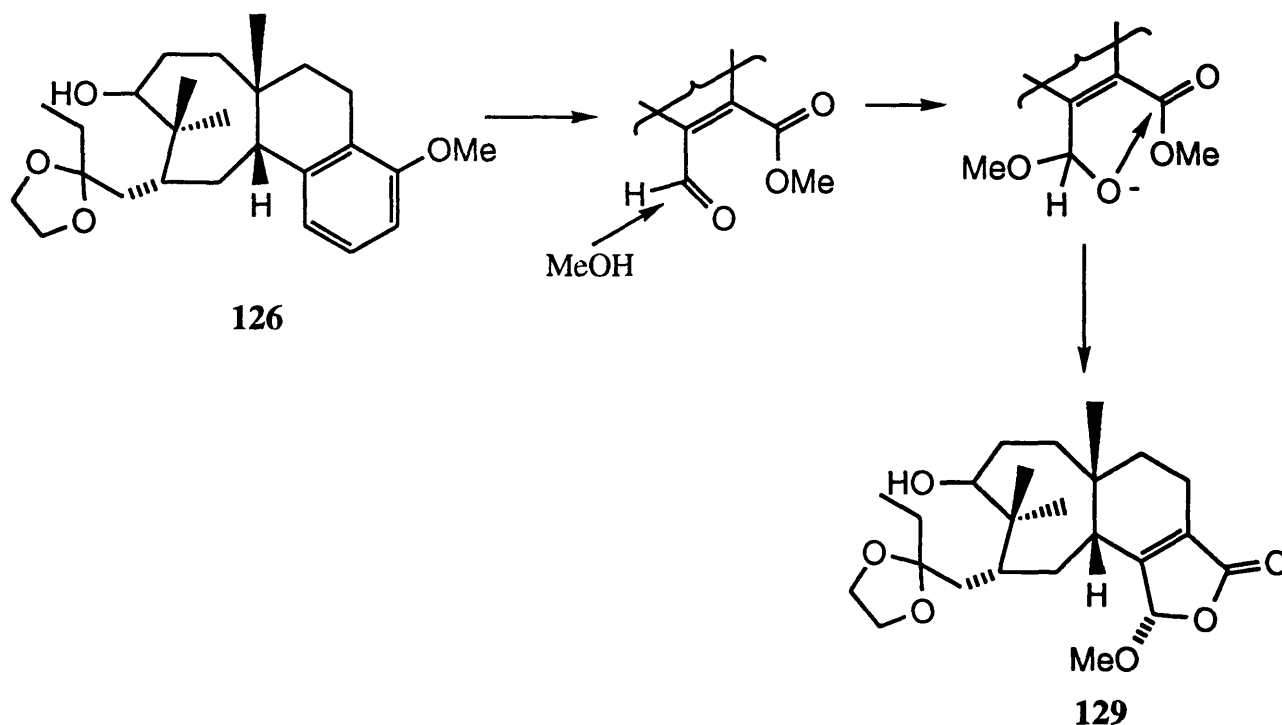
Scheme 64: Various reaction conditions for the ozonolysis of alcohol **126**.

Interesting observations were gathered from an analysis of the reaction via thin layer chromatography. In all cases except for the reaction leading to lactone **131**, the spot viewed immediately proceeding the addition of the reducing agent remained unchanged for the duration of the time that the reaction was stirred. The isolated products were identical, as viewed by thin layer chromatography, to the initial products of the ozonolysis. This observation could suggest two possibilities: (1) this ozonolysis reaction did not proceed through the ozonide, but instead formed the products directly in the reaction mixture, or (2) the reduction of intermediate ozonides occurred immediately at -78 °C upon the addition of a reducing agent.



Scheme 65: Previous examples of ozone cleavage of oxy-aromatic rings.

Direct ozonolysis of anisole compounds have not been extensively used in synthesis; however, a few examples are found in the literature (Scheme 65). In his synthesis of strychnine⁸⁵, Woodward performed an ozonolysis on dimethoxy compound **132** to afford diester **133**. A similar reaction was performed on phenol **134**⁸⁶ where a reaction with ozone resulted in the formation of hemiacetal lactone **135**. The reaction mechanism, based on the work of Bell and Gravestock, proposed that the reaction proceeded through a zwitterion intermediate that cyclized to form a hydroperoxide which was reduced to form the ultimate product **135**.



Scheme 66: Possible mechanism for the formation of acetal lactone **129**.

⁸⁵Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749; *Tetrahedron*, **1963**, *19*, 247.

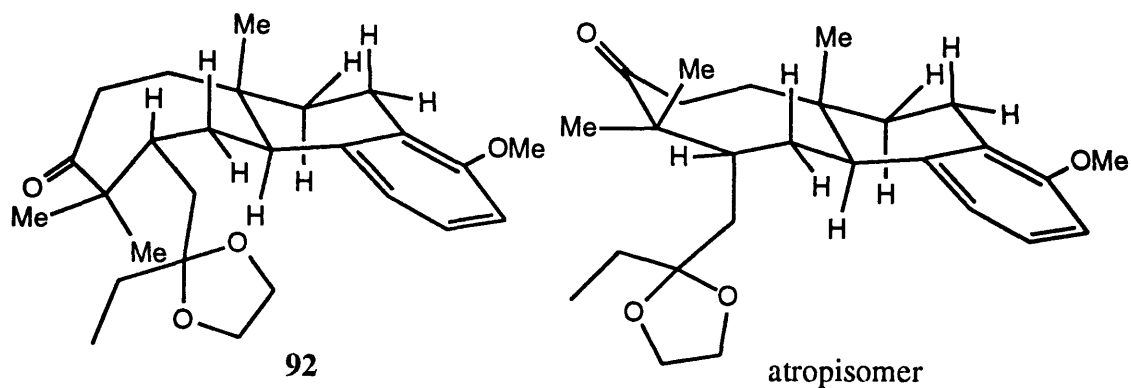
⁸⁶(a) Akita, H.; Mori, K.; Tahara, A. *Chem. Pharm. Bull.* **1977**, *25*, 974. (b) Akita, A.; Oishi, T. *Tetrahedron Lett.* **1978**, 3733.

Bell and Gravestock's mechanism, however, is not acceptable to explain the formation of acetal lactone **129**. A more likely mechanism, shown in Scheme 66 forms the hemiacetal of the aldehyde with methanol, and the resulting free alkoxide attacks the ester which results in the formation of acetal lactone **129**. This mechanism, however, does not explain the observation that when sodium borohydride is added as the reducing agent, no products resulting from the reduction of the aldehyde are observed.

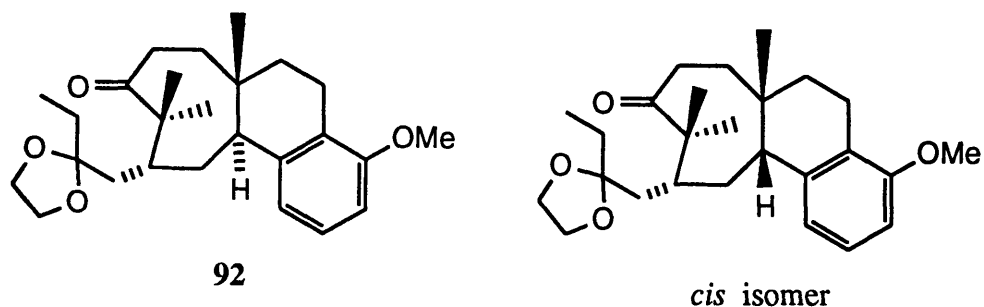
5.2 Synthesis of *cis* -BC Analogs

Although successful cleavage of the aromatic ring had now been accomplished, a route to directly functionalize the ozonolysis products to form the C-ring functionality in taxusin was not apparent. At this point; however, an interesting discovery was found. When alcohol **126**, obtained from the ring cleavage reaction of cyclobutane intermediate **93** with excess lithium and ammonia, was oxidized with pyridinium chlorochromate on neutral alumina in dichloromethane, the expected *trans* -cyclooctanone **92** was not isolated. Instead, a different ketone isomer was obtained, and according to mass spectroscopy, the

Theory I



Theory II



Scheme 68: Theories explaining new isomer.

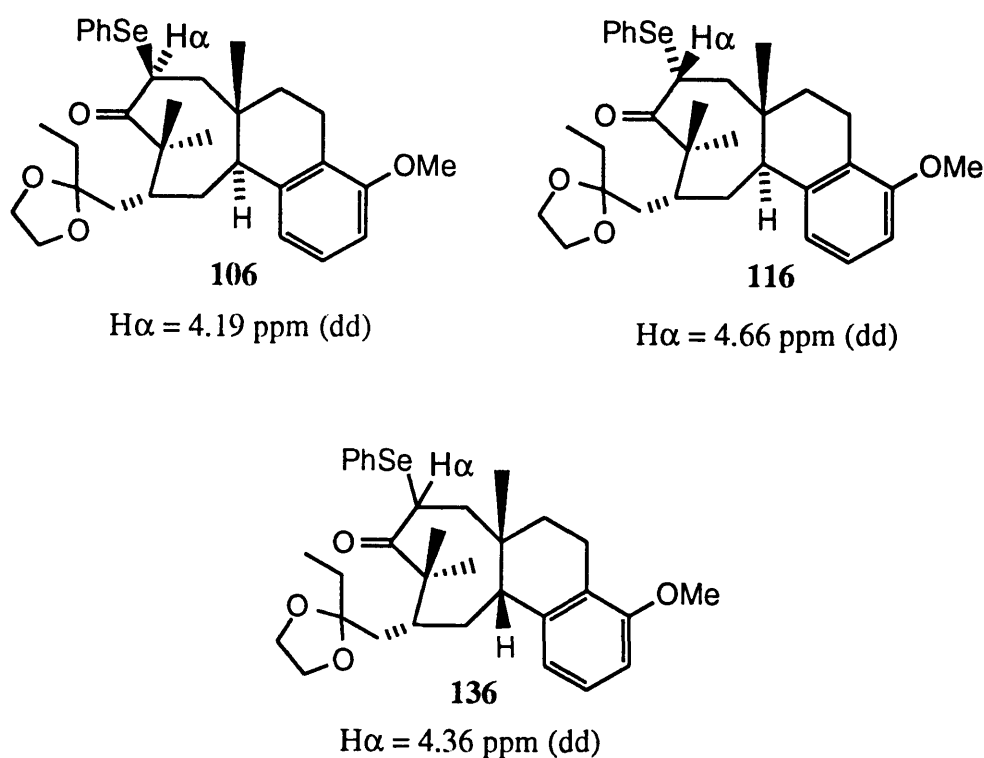
ketone possessed an identical molecular weight as *trans* -cyclooctanone **92**. In an effort to identify the new product, two hypotheses as were constructed (Scheme 68): (1) the new ketone existed as a different atropisomer resulting from the ketone in the eight-membered ring being held in a rigid position that was pointing toward the C(8) methyl group, instead of away from it as was determined in the X-ray structure of α -phenylselenide **106** or (2) the ring juncture C(3) proton was now *cis* to the C(8) methyl group, instead of the previously determined *trans* juncture for compound **92**. The first hypothesis was derived from Paquette's studies toward taxane synthesis, where it was found that his 9-membered ring system could exist as different atropisomers which could be interconverted thermally.⁸⁷ The second hypothesis stemmed from work by Swindell where he found that his *trans* -B-C ring system, which consisted of a double bond within the eight-membered B-ring, was readily isomerized to form the *cis* -B-C system.³⁶

In order to ascertain which of these hypotheses were correct, the α -phenylselenide compound was formed from the newly obtained isomer. This was expected to definitively distinguish between the two theories, because, since both compounds under Theory I would proceed through identical enolates, both compounds would form the same α -phenylselenide compound, *i.e.* α -phenylselenide **106**. Under Theory II, each isomer was expected to result in the formation of a different isomer.

The α -phenylselenide compound was formed using an identical procedure as that used for the formation of α -phenylselenide **106**. Therefore, the newly obtained ketone isomer was dissolved in tetrahydrofuran and cooled to -78 °C. Lithium bis(trimethylsilyl)amide was then added, and the reaction was warmed to 0 °C where it was stirred for two hours. After recooling to -78 °C, a solution of phenylselenium chloride in tetrahydrofuran was added via cannula, the reaction was warmed to room temperature, and was quenched by the addition of a solution of saturated sodium bicarbonate. After isolation

⁸⁷Paquette, L. A.; Zhao, M.; Fredrich, D. *Tetrahedron Lett.* **1992**, 33, 7311.

via preparative chromatography, the compound was determined to be different than both previously formed α -phenylselenium compound diastereomers. This was evidenced by observing the chemical shifts of the proton α to the selenide group in the ^1H NMR spectrum (Scheme 69). The $\text{H}\alpha$ proton in α -phenylselenide **106** had a chemical shift of 4.19 ppm while the C(10) epimer of compound **106**, α -phenylselenide **116** possessed a chemical shift of 4.66 ppm. α -Phenylselenenylketone **136** which resulted from substitution of the new isomer, compound **137**, had a chemical shift of 4.36 ppm. This result definitively determined that the new ketone isomer was, in fact the *cis* isomer, ketone **137**.



Scheme 69: Comparison of α -phenylselenide isomers.

The formation of the new, *cis* -B-C ring juncture was a very unexpected result, as three years of studies on the *trans* -ring system had never resulted in the formation of any *cis* isomers. At one point, efforts had been undertaken to form the *cis* -ketone isomer **137** from cyclobutane compound **93** through reductive techniques, as it was expected that the

cis system would possess less strain than the *trans* system, and fragmentation of the molecule during A-ring annulation attempts would pose less of a threat. However, reductive attempts to form the *cis* system through the use of hydrogenation techniques, samarium(II) iodide,⁸⁸ and tri-*n*-butyltin hydride as a radical agent, were unsuccessful; all resulting in the total re-isolation of starting material.

In order to gain insight into this reaction, suggesting reasons why stoichiometric metal in liquid ammonia results only in the formation of the *trans*-bicycle, while excess metal in liquid ammonia results only in the isolation of the *cis*-bicycle, the mechanism of the reaction must first be studied. An Organic Reactions review by Caine compiles much of the data of lithium and liquid ammonia reductions of carbonyl compounds that is relevant to this study.⁸⁹ The mechanism for the reduction of cyclobutane **93** is analogous to that for the reduction of α - β unsaturated carbonyl compounds, because the π -system of the cyclobutane bond overlaps with the π -systems of both the ketone and the aromatic ring. It is well known that metals in liquid ammonia readily transfer electrons into antibonding π -orbitals of conjugated systems resulting in the formation of radical anions.⁹⁰ This is the first step of the reduction of cyclobutane compound **92**, which accepts an electron into its ketone π -system, forming radical anion **138**, which results in the homolytic cleavage of the cyclobutane bond to form an enolate and a benzylic radical (Scheme 70).⁹¹ Because of the presence of the benzylic radical, the reduction potential of intermediate **139** is only slightly lower than that of the starting material **93**.^{92,93} Therefore, **139** accepts a second electron

⁸⁸(a) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841. (b) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15.

⁸⁹Caine, D. *Organic Reactions* **1976**, *23*, 1.

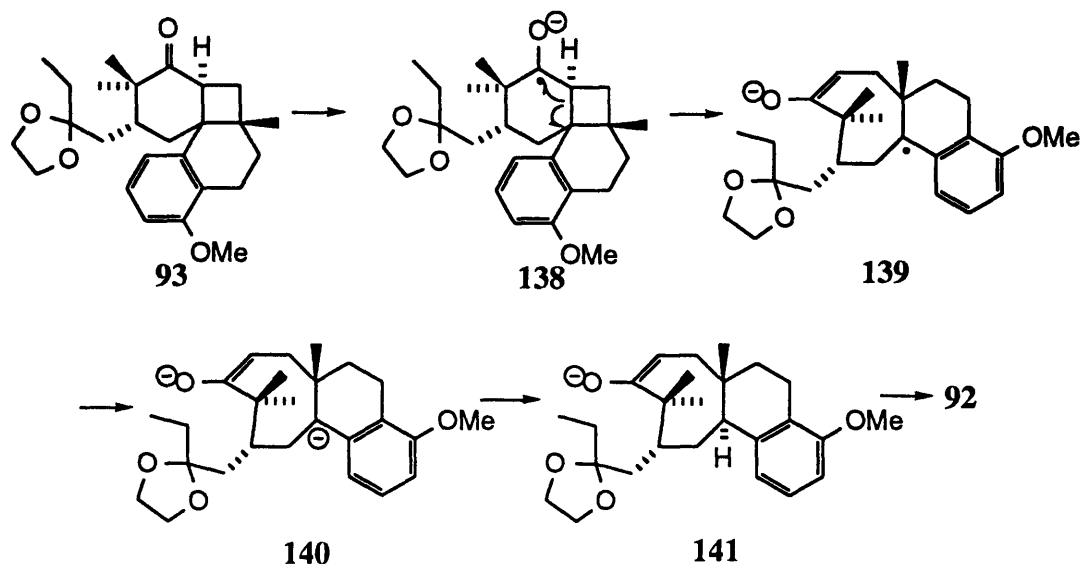
⁹⁰(a) Willstatter, FR.; Seitz, F.; Bumm, E. *Chem. Ber.* **1928**, *61*, 871. (b) Michaelis, L.; Schubert, M. *P. Chem. Rev.* **1938**, *22*, 437.

⁹¹(a) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3054. (b) Stork, G.; Darling, D. *J. Am. Chem. Soc.* **1960**, *82*, 1512. (c) Stork, G.; Darling, D. *J. Am. Chem. Soc.* **1964**, *86*, 1761.

⁹²Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783.

⁹³As compared to alkyl-substituted enone systems where the second electron transfer step requires a potential more negative than -3.0 volts versus a saturated calomel electrode (sce). Therefore, a free dianionic species is probably not formed during a metal-ammonia reduction of aliphatic enones. See Ref. 92.

into its π -system forming dianion **140**,⁹⁴ which is immediately protonated by ammonia to form enolate **141**.^{9,95}



Scheme 70: Lithium / liquid ammonia reduction mechanism.

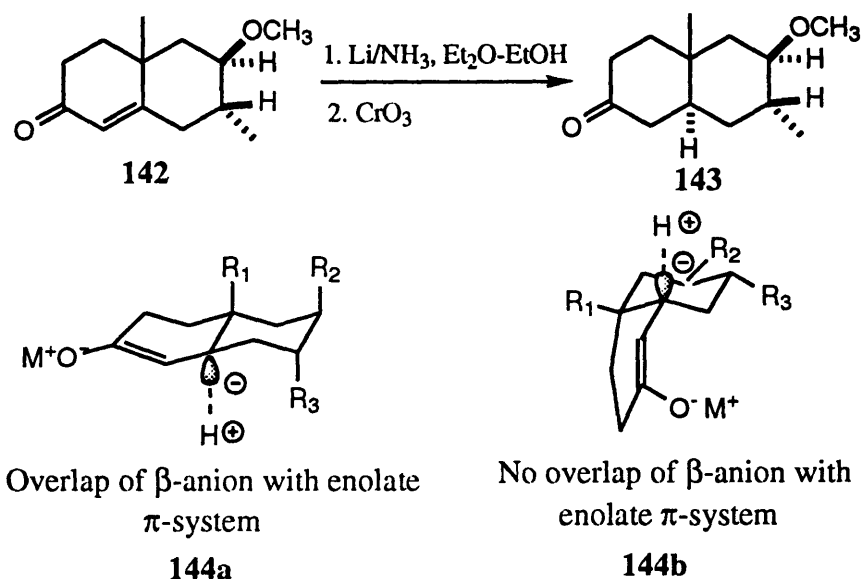
The stereochemical outcome of the metal-ammonia reduction is determined by the β -protonation step, which usually, when located at the juncture of a six-membered ring, results in the formation of the more thermodynamically stable reduction product. However, many exceptions to this trend has been seen in reductions of members of the octalone series.⁹ An example of this is seen in the reduction of octalone **142**, where a reduction with lithium-ammonia-ethanol, followed by oxidation with chromic acid, results in the formation of *trans*-decalone **143** (Scheme 71). This is a surprising result considering that the *cis*-decalone isomer of **143** is 2 kcal/mol more stable than the *trans*-isomer. In order to understand this outcome, the possible protonation transition states are considered where the β -carbon anion is pyramidalized.⁹⁶ In transition state **144a**, which

⁹⁴Hamrick, P. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 493.

⁹⁵Zimmerman, H. E. *Molecular Rearrangements*, Pt. I, P. de Mayo, Ed., Interscience Publishers, New York, **1963**, p. 345.

⁹⁶(a) Robinson, M. J. T. *Tetrahedron* **1965**, *21*, 2475. (b) House, H. O. *Modern Synthetic Reactions*, 2nd Ed., Benjamin, Menlo Park, CA, **1972**, Ch. 3. (c) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. P. *J. Am. Chem. Soc.* **1963**, *85*, 2091. (d) Cram, D. J. *Fundamentals of*

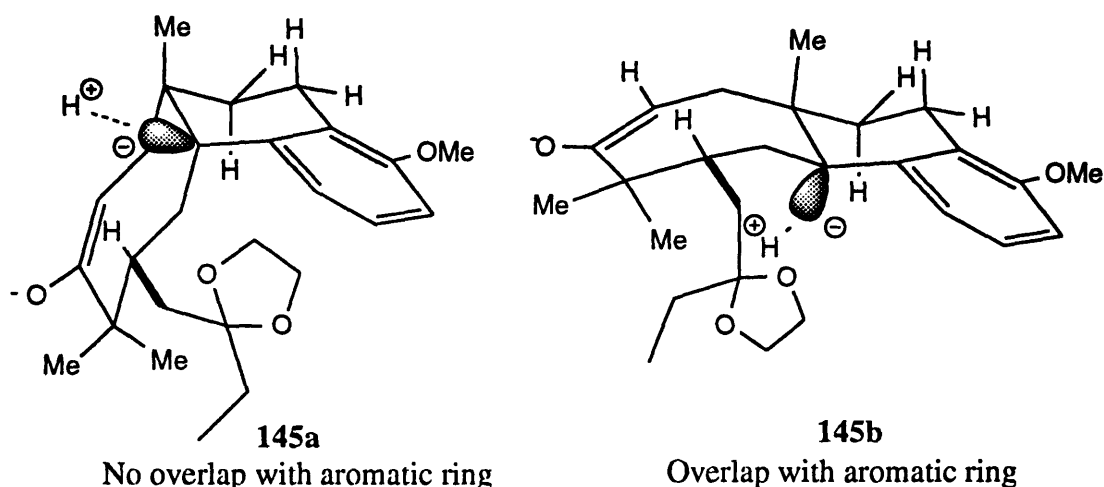
leads to the major isomer, the orbital of the developing C-H bond overlaps with the π -system of the enolate. In **144b**, however, no overlap is possible, and, since the β -anion is protonated by ammonia more rapidly than equilibration can occur, the less stable *trans*-isomer is the major product. From this analysis, it can be determined that the *trans*-isomer is being formed through a kinetic preference.



Scheme 71: Comparison of protonation transition states for octalone **142**.

A similar explanation can be used to explain the observed stereochemical outcome for the lithium-ammonia reduction of cyclooctanone **93** using nearly a stoichiometric amount of lithium metal. When the two possible protonation transition states, where the β -anion is pyramidalized, are compared, the preference for the *trans*-isomer is evident (Scheme 72). In transition state **145b**, which leads to the formation of the *trans*-isomer, the orbital of the developing C-H bond overlaps quite well with the aromatic ring. Oppositely, in transition state **145a**, which leads to the *cis*-isomer, no overlap is possible.

Therefore, when only a stoichiometric amount of metal is present in the reaction mixture, the cyclobutane is readily reduced, forming dianion intermediate **145b**, which is immediately protonated forming, as the only stereoisomer, the *trans*-ketone **92**. Therefore, it can be concluded that the *trans*-stereoisomer is the kinetic product.

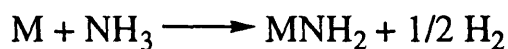


Scheme 72: Possible protonation transition states for reduction of cyclobutane **93**.

An explanation for the isolation of the *cis*-isomer when many equivalents of lithium are used in the reaction mixture is less straightforward.⁹⁷ Obviously, it can be stated that the *cis*-ketone isomer is the thermodynamically more stable isomer, and that the conditions of the lithium-ammonia reduction, where excess lithium is present, are causing equilibration to occur. One explanation for this result is derived from the fact that metals react slowly with ammonia to form metal amides and hydrogen.⁹⁸ The amount of metal amide in solution can be significant when concentrated solutions

⁹⁷It should be noted that the isolation of the *cis*-isomer cannot be explained by a change in reducing metal (from calcium to lithium) as the *cis*-isomer is formed using both metals. When *trans*-Ketone was resubjected to the metal-ammonia conditions, the *cis*-isomer was isolated.

⁹⁸(a) Dewald, J. F.; LePoutre, G. *J. Am. Chem. Soc.* 1954, 76, 3369. (b) Jolly, W. L.; Prizant, L. *Chem Commun.* 1968, 1345.



of metals are used, and this reaction can be strongly catalyzed by transition metals such as iron, cobalt, nickel, and by ultraviolet light.⁹⁹ Therefore, the equilibration of the kinetic *trans* -product may be the result of a deprotonation of the benzylic proton which epimerizes to form the more thermodynamically more stable *cis* -product under the conditions. It is interesting to note that it seems that the presence of the methoxy group on the aromatic ring is greatly enhancing the equilibration mechanism, as when the cyclobutane compound without the aromatic ring is subjected to reduction with excess lithium in liquid ammonia, no *cis* -isomer is observed.

When the reduction of cyclobutane **93** is performed with excess lithium in liquid ammonia, the compound is exhaustively reduced to form alcohol **126**. This occurs through protonation of the resulting enolate, followed by an electron transfer to the π -system of the resulting ketone. The presence of the alcohol may be enhancing the equilibration by coordinating lithium or lithium amide, thereby catalyzing the deprotonation of the benzylic proton of the *trans* -isomer.

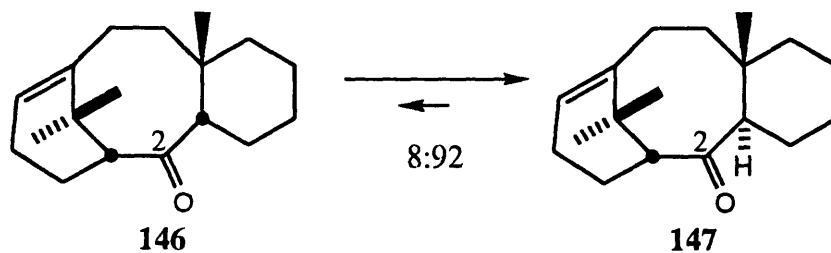
⁹⁹Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, Wiley, New York, 1967.

Chapter 6. Efforts Toward the A-ring Annulation of the *cis* -BC Ring System

6.1 Efforts Toward the Tandem-aldol Payne Rearrangement

The formation of the new *cis* -B-C ring system coupled with the failures of the A-ring annulation on the bicyclic *trans* -compounds, created hope that the *cis* compounds might possess a significantly different conformation upon which the cyclization might be successful. This hope was derived from modeling studies which had suggested that the *cis* compounds might possess less ring strain energy than their *trans* counterparts; therefore, it was expected that fragmentation would be less of a problem. Additionally, modeling studies suggested that the *cis* compounds might exist in a conformation that would possess a lower energetic barrier leading to the formation of the A-ring.

Although this strategy would result in the incorrect stereochemistry across the B-C ring juncture, observations by Swindell showed that the *trans* B-C ring juncture could be formed from the *cis* B-C ring juncture on the fully cyclized ABC system (Scheme 73). These early studies on taxane systems by Swindell¹⁰⁰ documented, through epimerization

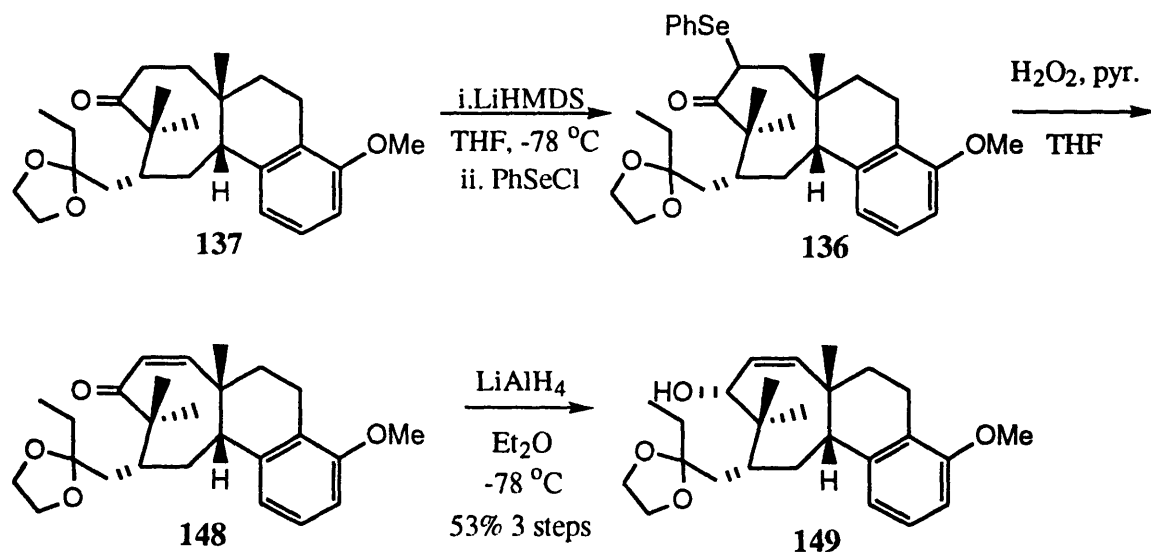


Scheme 73: Epimerization study on taxane tricyclic system.

¹⁰⁰Swindell, C. S.; Patel, B. P. Tetrahedron Lett. **1987**, 28, 5275.

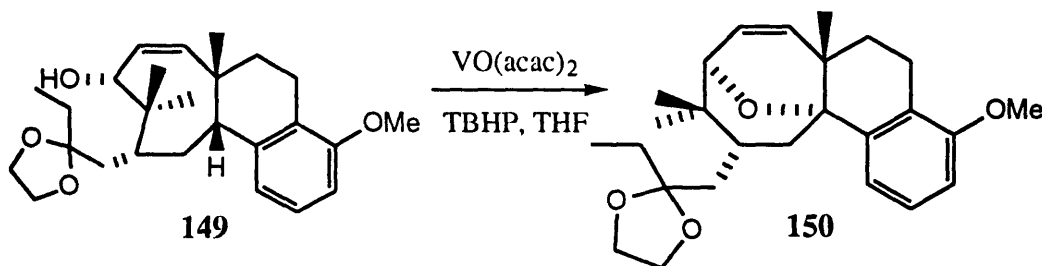
studies, that a fully cyclized taxane framework **146**, with a *cis* B-C ring juncture and a C(2) ketone functionality, readily epimerized to the *trans* B-C ring juncture **147** upon subjection to sodium methoxide. Therefore, it was expected that if the A-ring annulation was successful on a bicyclic *cis* compound the resulting tricyclic *cis* compound could be readily epimerized to afford the desired tricyclic *trans* compound.

Therefore, efforts to perform the tandem-aldol Payne rearrangement on the *cis*-bicycle were undertaken. Towards this goal, α -phenylselenenylketone **136**, the stereochemistry of which was not determined, was converted to enone **148** through an oxidation of the selenide to the selenoxide with hydrogen peroxide in tetrahydrofuran and pyridine, which readily eliminated at room temperature to afford an inseparable mixture of ketone **137** and enone **148** (Scheme 74). All efforts to cause the epoxidation of enone **148** with nucleophilic conditions were unsuccessful as in the case of the *trans*-enone; consequently, enone **148** underwent 1,2-reduction with lithium aluminum hydride to afford allylic alcohol **149** in 53% for three steps from ketone **137**.



Scheme 74: Elaboration of *cis*-ketone **137**.

The stereochemistry of newly-formed allylic alcohol **149** was assumed to be α as shown in Scheme 74 for reasons identical to those used toward the formation of the previously-formed *trans*-allylic alcohol; consequently, epoxidation was attempted with vanadyl acetylacetonate. Unfortunately, reaction of allylic alcohol **149** with vanadyl acetylacetonate did not result in any appreciable formation of epoxide. The reaction was worked up before all of the starting material had reacted, and an ^1H NMR spectrum revealed that an additional set of olefinic protons were present possessing a similar coupling pattern as the starting material olefinic coupling pattern. Therefore, it was postulated that cyclic ether **150** was being formed in a similar fashion as cyclic ether **112**; however, in this case the cyclization reaction was occurring more quickly than the epoxidation. When the mixture was resubmitted to the reaction conditions, however, the products decomposed (Scheme 75).

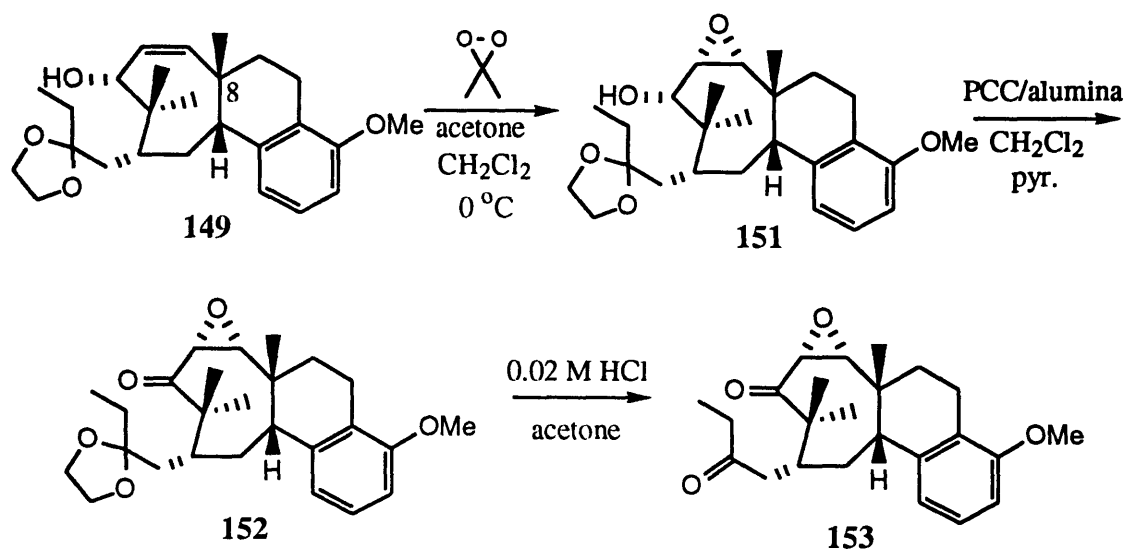


Scheme 75: Attempted epoxidation of allylic alcohol **149**.

Because the epoxidation with vanadyl acetylacetonate was not successful, the epoxidation was performed with dimethyl dioxirane, known to be very sensitive to steric constraints,¹⁰¹ in an acetone solution and dichloromethane (Scheme 76). The reaction was assumed to proceed with the desired stereochemistry as shown in epoxy alcohol **151**, with the oxidation occurring on the face opposite the C(8) methyl group. Only one epoxide isomer was formed during the reaction in 85% yield. The resulting epoxy alcohol **151**,

¹⁰¹(a) Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, 52, 746. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, 53, 3437.

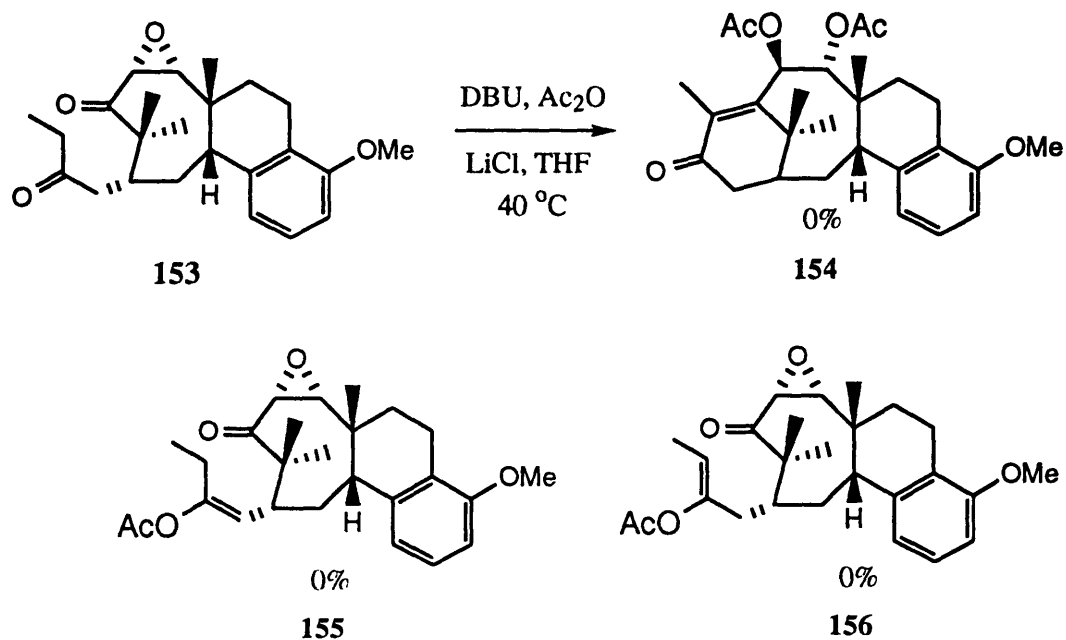
was oxidized to form epoxy ketone **152** with pyridinium chlorochromate on neutral alumina in dichloromethane. Although the reaction occurred slowly, being completed after 36 h, the epoxy ketone **152** was isolated in 80% yield. The ketal protecting group was then removed through a deketalization reaction with 0.02 M hydrochloric acid in acetone to yield epoxy diketone **153**.



Scheme 76: Elaboration of allylic alcohol **149**.

With the completion of the synthesis of epoxy diketone **153**, the tandem-aldol Payne rearrangement was attempted (Scheme 77). To epoxy diketone **153** was added a solution of tetrahydrofuran saturated with lithium chloride, acetic anhydride, and diazabicycloundecane. The reaction was heated to 40 °C and was stirred overnight, at which time analysis by thin layer chromatography revealed that only starting material was present. Therefore, additional acetic anhydride and diazabicycloundecane was added until 150 equivalents of each reagent was present. The reaction was stirred under these conditions for two days, after which time the reaction was worked up, and the product was isolated. Analysis by ^1H NMR revealed that only starting material, epoxy diketone **153**,

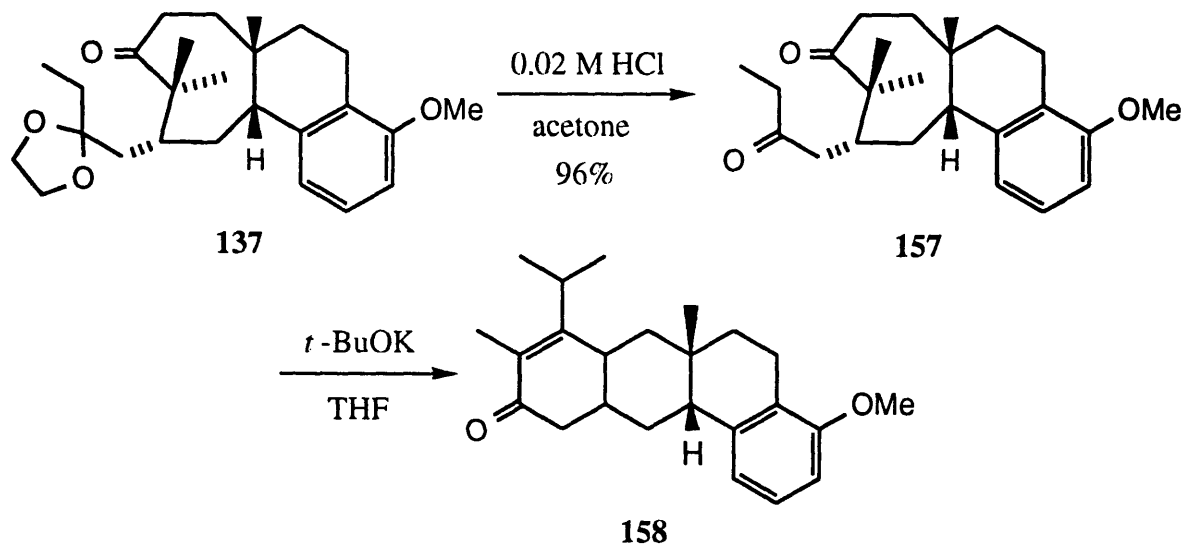
was present. Again, this was very unexpected, as not only did the expected tricyclic compound **154** fail to form, but any apparent amount of enol acetate **155** or **156** also was not seen.



Scheme 77: Attempted tandem-aldol Payne rearrangement.

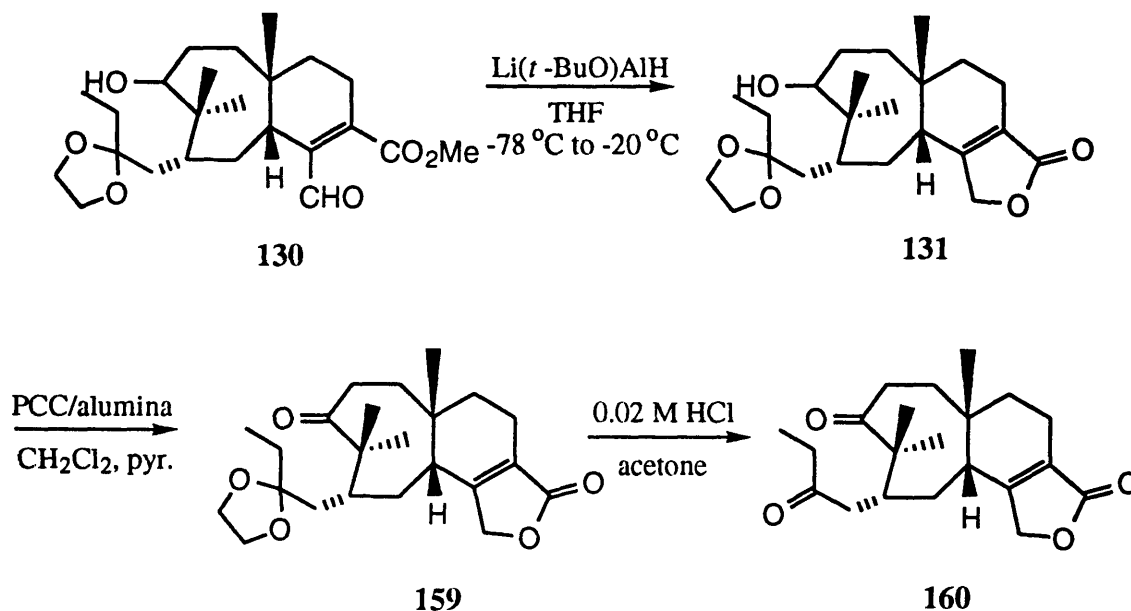
6.2 Alternative Strategies

Although the tandem-aldol Payne rearrangement on the *cis*-hydroxy diketone **153** was unsuccessful, efforts were undertaken on other *cis*-compounds to ascertain if other *cis*-compounds possessed a higher propensity to cyclize. The first of these systems was the simple *cis*-ketone **137** (Scheme 78). Toward this goal, the ethylene ketal on the C(1) side chain *cis*-ketone **137** was removed via a transketalization procedure using 0.02 M hydrochloric acid in acetone. Cyclization was then attempted on the resulting *cis*-diketone **157** by the addition of *tert*-butoxide to a solution of the compound in tetrahydrofuran. The reaction proceeded smoothly to one product, which, upon workup, was proven by ^1H NMR analysis to be tetracyclic enone **158**, isolated a single diastereomer. This reaction was analogous to the undesired retro-Michael fragmentation that had occurred on the *trans*-diketone.



Scheme 78: Retro-Michael fragmentation of the *cis*-diketone.

With exhaustive efforts towards a successful annulation of the A-ring on both the *cis* and *trans* bicyclic systems resulting in either undesired fragmentation reactions or the occurrence of no reaction, the final endeavor that was undertaken was an attempt to cyclize a compound where the aromatic ring had been cleaved (Scheme 79). Therefore, conjugated



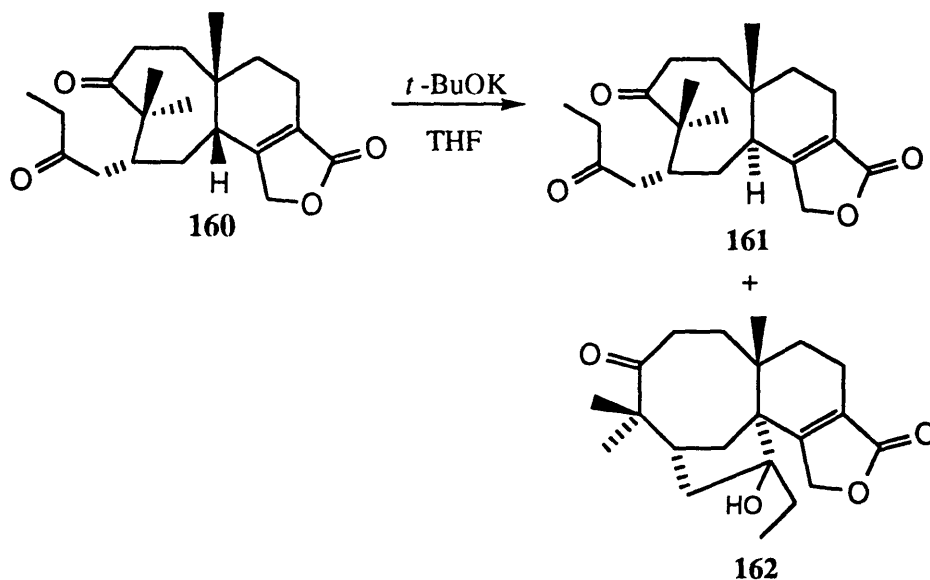
Scheme 79: Elaboration of ester aldehyde **130**.

aldehyde ester **130** was converted to the lactone through the selective reduction of the aldehyde functionality without the additional 1,4- or 1,2-reduction of the α,β -unsaturated ester group. This was accomplished with the use of the mild reducing agent lithium tri(*tert*-butoxy)aluminumhydride¹⁰² which was added at -78°C as a 0.25 M solution in tetrahydrofuran. The reaction was warmed to -20°C at which time all of the starting material had reacted. Lactone **131** was then isolated via workup and flash column chromatography to afford the desired compound in 97%. Although lactone **131** could be formed from alcohol **126** in a single step, it could be formed in a higher overall yield in

¹⁰²(a) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1956**, *78*, 752. (b) Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 5372. (c) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 5377. (d) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

two steps from ester aldehyde **130**. The alcohol functionality was then oxidized with pyridinium chlorochromate on neutral alumina in dichloromethane and pyridine to afford keto-lactone **159** in 98% yield. The ketal was then removed using the usual method of transketalization with 0.02 M hydrochloric acid in acetone to afford diketone **160**, which was prepared to undergo cyclization.

Annulation of the A-ring of diketolactone **160** was then attempted via the usual method through the creation of a solution of compound **160** in tetrahydrofuran. Potassium *tert*-butoxide was then added in a single portion, and the reaction was stirred at room temperature overnight at which time analysis via thin-layer chromatography revealed that all of the starting material had reacted to form two products (Scheme 80). It was postulated that the first compound, which was the minor product, was the C(3) epimer **161** resulting



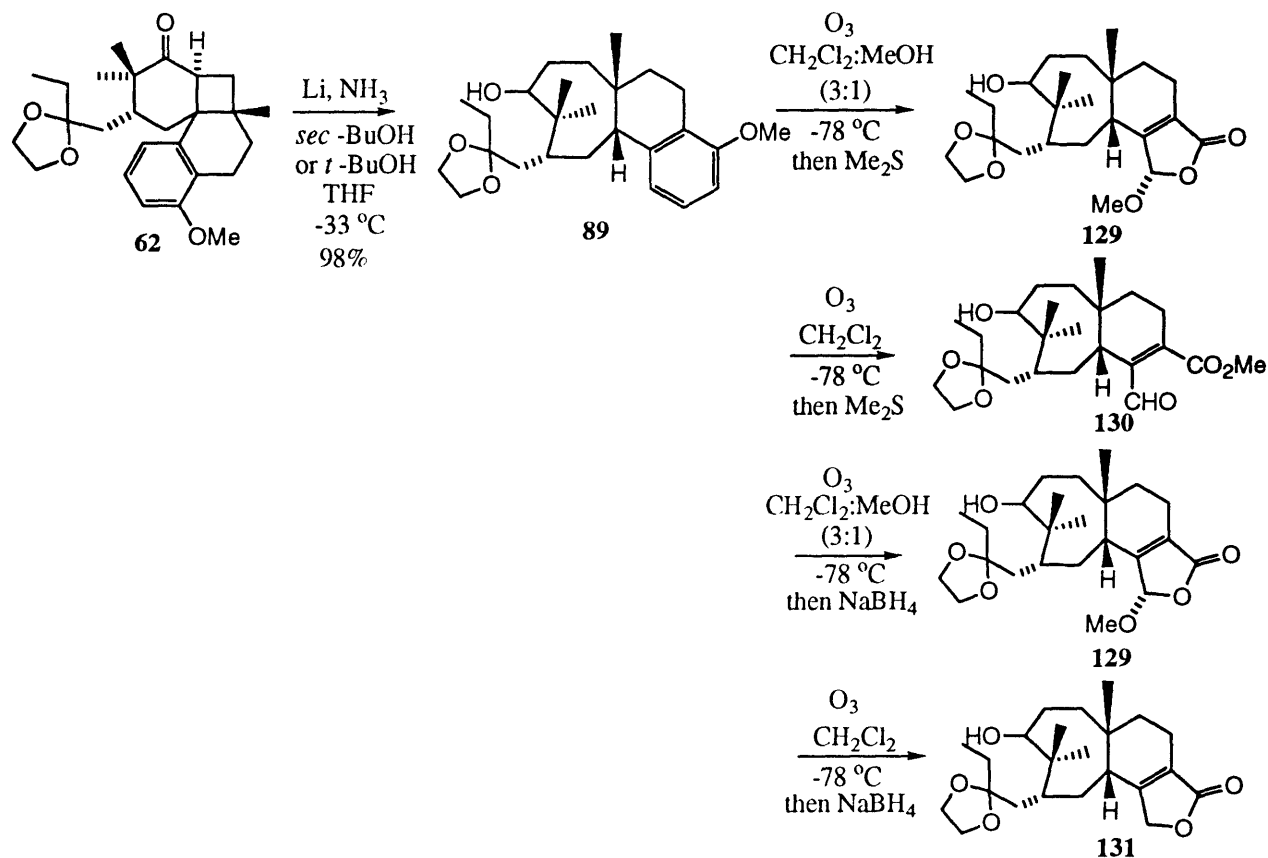
Scheme 80: Attempted A-ring annulation of diketolactone **160**.

from deprotonation of the benzylic position. Evidence in the ^1H NMR that suggested epimerization had occurred was the downfield shift of the protons on the lactone. These protons possessed a similar splitting pattern, as they couple to the proton at the ring juncture. The major isomer was postulated to be tetracycle **162**, which was isolated as a

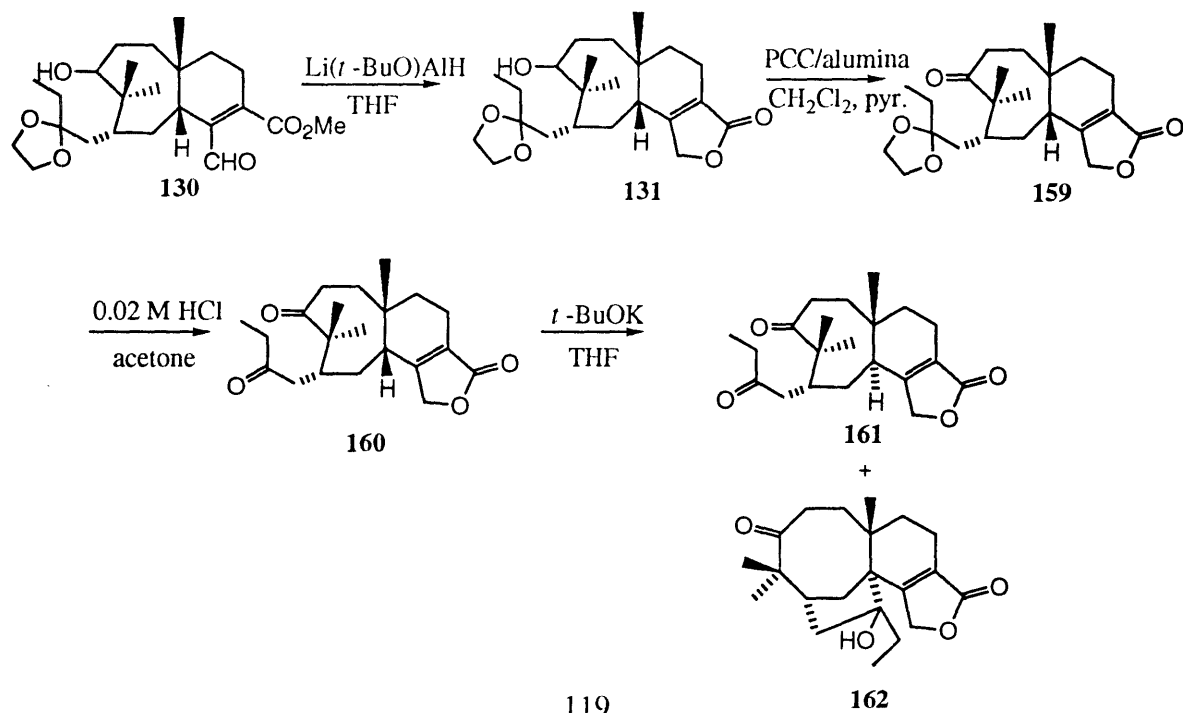
single diastereomer. Although we were not certain of the formation of **162**, NMR analysis revealed that the proton at the ring juncture was no longer present, which suggested that this position had been alkylated. Since an anion at the ring juncture could attack only the C(11) ketone or the C(13) ketone, and the C(14) protons had been altered, the formation of **162** was hypothesized.

6.3 Summary

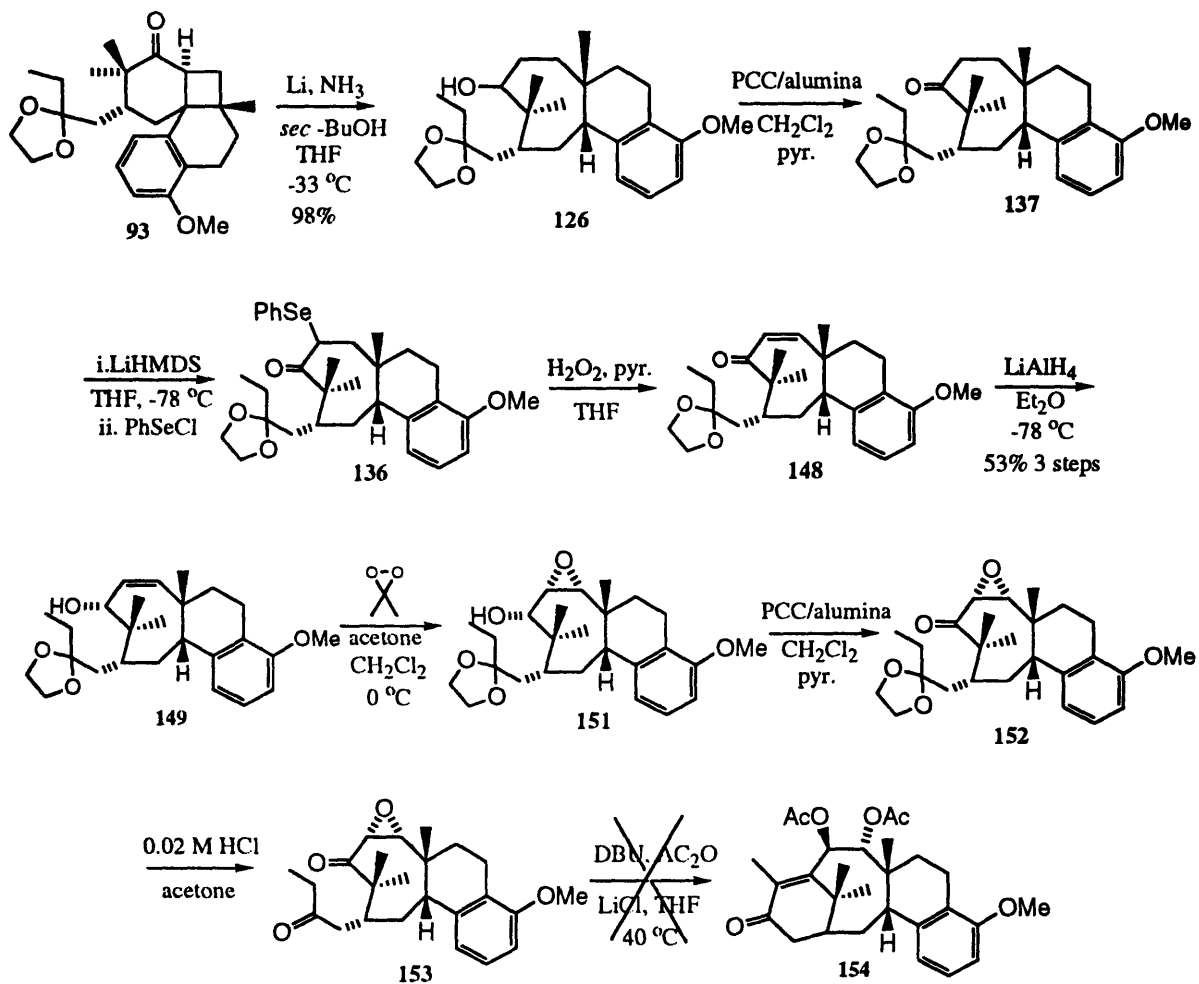
Cleavage of the Anisole Ring



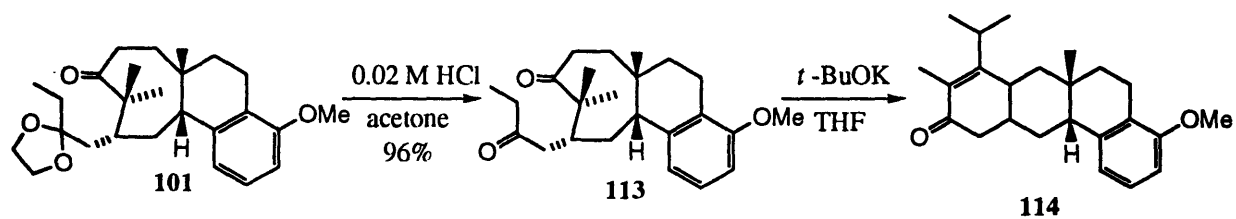
Efforts to cyclize lactone derivative



Synthesis of *cis*-analogs



Retro-Michael Fragmentation of *cis*-Cyclooctanone



Chapter 7. Future Prospects

During the course of this project, we have had many successes, and have developed novel chemistry including the stereochemical reversal of the photocyclization, the novel cleavage of the anisole ring using ozone, and the discovery that both of the possible B-C ring juncture stereoisomers could be obtained as a single diastereomer by altering the amount of lithium or calcium metal used in the dissolving metal reaction. However, the fact that all of the many attempts to bring about a successful A-ring cyclization resulted in either no reaction or an undesired fragmentation is very troublesome. As was previously mentioned, Swindell has hinted that problems might arise in the course of the A-ring annulation when the conformation of the C-ring is altered. Further evidence of problems that could be inherent in the A-ring cyclization strategy is found in the fact that recently, Swindell abandoned this synthetic route, stating that its failure was brought about because of difficulties found "in modifying his route to incorporate C-ring functionality required by natural taxanes."¹⁰³

Although this recent revelation does not bode well for the success of a strategy that incorporates an A-ring annulation of any of our aromatic substituted intermediates, this does not mean that success cannot be found in our strategy. The key to this project's success should be found in the cleavage of the aromatic ring prior to the cyclization of the A-ring, and discovering what functionality can be tolerated on the C-ring. Therefore, it can probably be assumed that the inclusion of a double bond within the C-ring will probably not result in the success of the cyclization.

¹⁰³Swindell, C. S.; Chander, M. C. *Tetrahedron Lett.* **1994**, *35*, 6001.

Experimental Section

General Procedures: Reaction mixtures were stirred magnetically unless otherwise indicated. All moisture and / or air sensitive reactions were carried out under a positive pressure of argon, and were performed in glassware that was oven and / or flame dried. Solvents and liquid reagents were transferred via syringe or cannula. Reactions were monitored by thin layer chromatography as described below. Organic solvents were removed through concentration on a Büchi rotary evaporator at 20 - 40 mmHg.

Materials : Commercial solvents and reagents were used without further purification with the following exceptions:

Solvents

Benzene was distilled under argon from calcium hydride.

Deuteriochloroform was stored over granular anhydrous potassium carbonate.

Dichloromethane was distilled under nitrogen from phosphorus pentoxide.

N, N - Dimethylformamide was stored over activated 4Å molecular sieves.

Ethyl Ether was distilled under argon from sodium benzophenone ketyl.

Hexanes were distilled under nitrogen from calcium hydride.

Pyridine was distilled under argon from calcium hydride.

Tetrahydrofuran was distilled under argon from sodium benzophenone ketyl.

Toluene was distilled under nitrogen from calcium hydride.

Reagents

N - Bromosuccinimide was recrystallized from hot water.

n - Butyllithium was titrated prior to use with *s* - butanol in tetrahydrofuran at 0 °C using 1,10 - phenanthroline as an indicator.¹⁰⁴

t - Butyllithium was titrated prior to use with *s* - butanol in ether at -78 °C using 1,10 - phenanthroline as an indicator.

Cuprous cyanide was dried under vacuum (0.5 mmHg) for 12 h prior to use.

Dimethyldioxirane was formed by stirring 21 mL acetone, 30 mL water, 18 g sodium bicarbonate, and 31.5 g oxone under house vacuum (~30 mmHg), and condensing the reagent in a -78 °C dry ice / acetone cold finger to form 0.08 - 0.11 M solution in acetone. The reagent was dried over magnesium sulfate before use.¹⁰⁵

Ethyl acetoacetate was dried over magnesium sulfate and distilled at 12 mmHg.

Lithium diisopropylamide was prepared by the addition of 2.55 M *n* - BuLi (5.88 mL) to a solution of *N,N* - diisopropylamine (2.31 mL) in THF (6.81 mL) at -78 °C followed by warming to 0 °C to form 15 mL 1.0 M reagent.

Lithium metal was stored under mineral oil and was washed with hexane, flattened, and cut into small pieces before use.

Methyl acetoacetate was dried over magnesium sulfate and distilled under argon.

Methyltriphenylphosphonium bromide was dried by azeotropic distillation with toluene.

Thiophene was distilled under argon over calcium hydride.

Phenylselenium chloride was formed by bubbling chlorine gas through a solution of diphenyldiselenide in hexane, and the resulting reagent was stored in a DynaQuip dry box.

Chromatography

Flash column chromatography was performed using EM silica gel of particle size 0.040 - 0.060 mm. HPLC grade solvents were used.

¹⁰⁴ Watson, S.C.; Eastham, J.F. *J. Organomet. Chem.* **1967**, *9*, 165.

¹⁰⁵ Murray, J. *Org. Chem.* **1985**, 2847.

Thin layer chromatography (TLC) was performed as an analytical tool using Baker high performance precoated glass silica gel (SiO_2 , approx. $5\mu\text{m}$ particle size) plates ($200\mu\text{m}$ thickness). The plates were assimilated with 254 nm fluorescent indicator. The procedure used was to elute using the solvent mixture indicated in the text, followed by an observation by illumination with a 254 nm ultraviolet light, and staining by dipping in either an ethanolic solution of 2.5% *p* - anisaldehyde (3.5 % sulfuric acid and 1.0 % acetic acid) or an ethanolic solution of phosphomolybdic acid (20% wt.) followed by heating on a hot plate.

Preparative thin layer chromatography was performed by using EM precoated silica gel plates (SiO_2 , 0.5 mm thickness) impregnated with 254 nm fluorescent indicator. The procedure followed was to elute with the solvent mixture indicated in the text, followed by observing the band with a 254 nm ultraviolet light. The desired band was scraped off the plate using a clean metal blade, and the silica gel was powdered and placed in a glass column. The product was extracted by several elutions with ether or dichloromethane.

Physical Data

Optical rotations were determined using a Perkin-Elmer 241 polarimeter using a sodium lamp (D line) at 23°C , and are reported in degrees. Concentration (c) is indicated as units of $10\text{ mg} / \text{mL}$.

Melting points were determined on a Fischer - Johns hot stage apparatus and are uncorrected.

IR spectra were recorded on a Perkin-Elmer spectrometer equipped with an internal polystyrene sample as a reference.

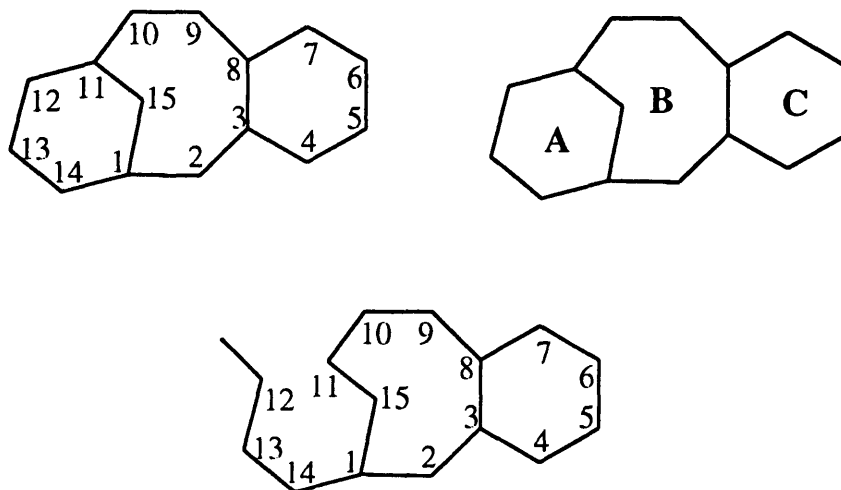
^1H NMR were recorded on either a Varian XL 300 MHz spectrometer, a Varian Unity 300 MHz spectrometer or a Varian VXR 500 MHz spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.0) using the residual chloroform signal (δ 7.26) as a standard. Multiplicities are reported in

the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), pd (pair of doublets), pq (pair of quartets), pdq (pair of a doublet of quartets), dd (doublet of doublets), ddd (doublet of doublets of doublets), *etc.*

^{13}C NMR were recorded on either a Varian 300 NMR at 75 MHz or a Varian 500 NMR at 125 MHz. The deuteriochloroform signal (δ 77.01) was used as a standard.

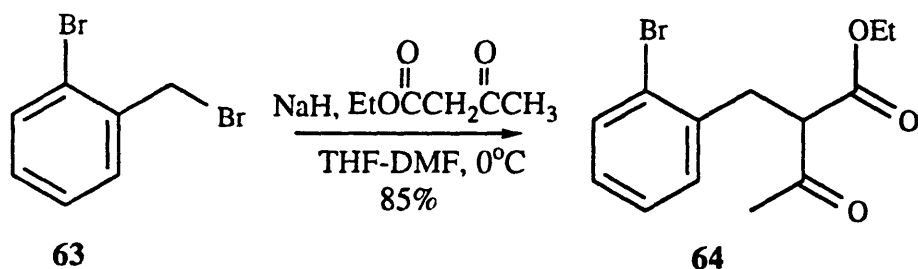
Mass spectra and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT System 8200, double focusing, magnetic sector, mass spectrometer. The spectra were recorded using either electron impact (EI), generating (M^++1), or fast atom bombardment (FAB) with sodium iodide in 3 - nitrobenzyl alcohol , generating ($M+\text{Na}^+$). Spectra were recorded in units of mass to charge (m/e).

Elemental analyses were performed by Galbraith Laboratories.



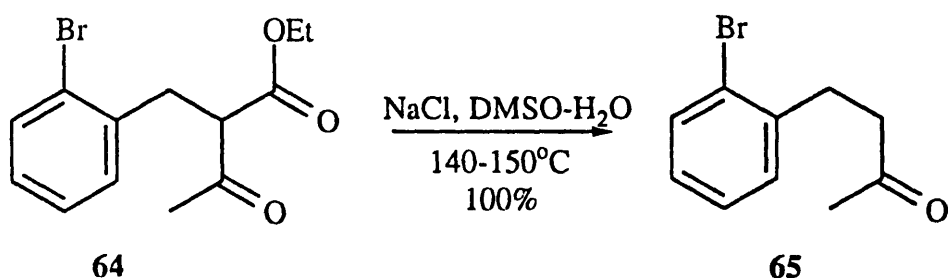
For the purposes of nomenclature and physical assignments, numbering of the taxane framework is presented in accord with the taxane structure shown in the above scheme for C(1) through C(14) and C(15). Hydrogen and methyl substituents attached to the taxane nucleus are designated according to position of attachment and projection of the substituent (α depicting below the plane of the taxane framework or below the plane of the page, and β depicting above the taxane framework or above the plane of the page). The

rings are designated A,B,and C as represented in the previous scheme, and in cases where the A ring is not intact, the taxane numbering still applies as depicted above.



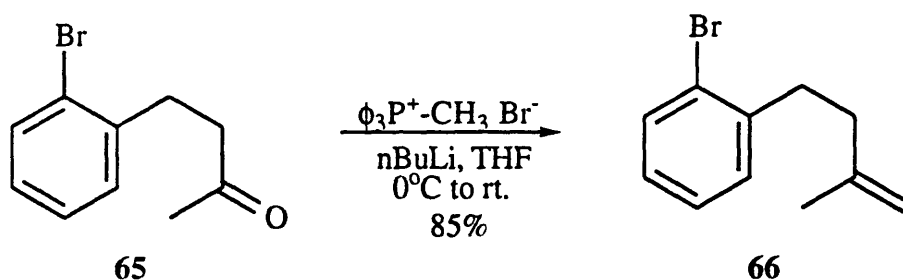
β-Ketoester 64:

Sodium hydride (0.92 g, 38 mmol) was weighed *in vacuo*, and to it was added 15 mL dry tetrahydrofuran to form a slurry which was slowly added via cannula into a solution of ethyl acetoacetate (5.0 g, 4.9 mmol) in 25 mL dry tetrahydrofuran and 40 mL *N,N*-dimethylformamide at 0 °C. After deprotonation, as evidenced by the cessation of hydrogen evolution, benzyl bromide (63) (8.0 g, 32 mmol) was transferred via cannula into the solution. The reaction mixture was then warmed to room temperature and stirred for two hours, at which time water was added. The tetrahydrofuran was then evaporated, and the mixture was extracted with 5% ether / hexane. The layers were separated, and to the aqueous layer were added more water and sodium chloride until saturation was apparent. The aqueous layer was then washed with 5% ether / hexane until no more product was present (8 x 25 mL), and the solvent was evaporated *in vacuo*. The crude product was distilled at 123 °C (0.7 mmHg) as a clear oil to yield 7.95 g (85%) of β-ketoester 64. *R*_f 0.60 (1:1 ether / hexane). ¹H NMR (250 MHz, CDCl₃) δ 7.53 (d, 1H), 7.24-7.05 (m, 3H), 4.14 (dq, 2H, *J* = 3.5, 5.3 Hz), 3.97 (dd, 1H, *J* = 6.8, 8.1 Hz), 3.26 (m, 2H), 2.23 (s, 3H), 1.20 (t, 3H, *J* = 7.2 Hz)



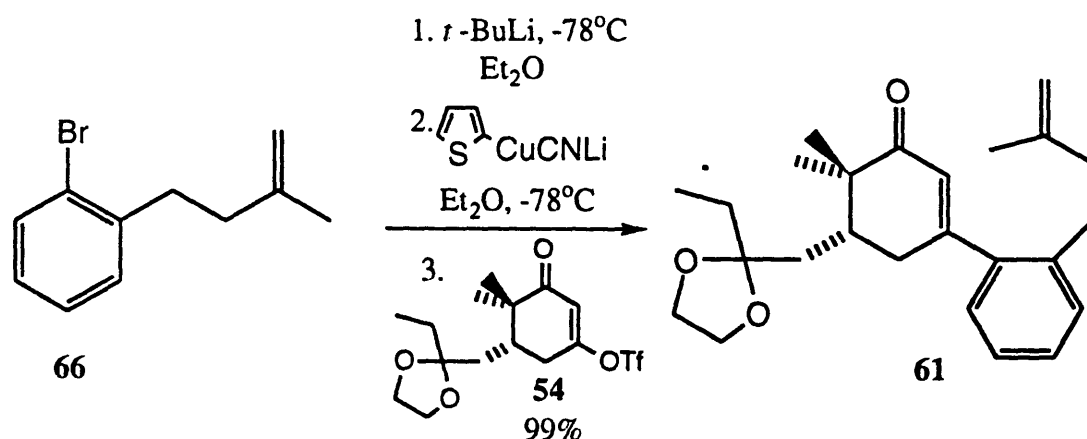
1-(o-Bromophenyl)-3-butanone **65**:

A mixture of the β -ketoester **64** (4.0 g, 13.4 mmol), lithium chloride (0.61g, 14 mmol), water (0.71 mL, 39 mmol), and dimethylsulfoxide (15 mL) was heated under argon with stirring for 15 hours at 140 - 150 °C, during which time there was a color change to reddish brown. The mixture was then cooled and diluted with water (25 mL), and sodium chloride was added until saturation was apparent. The solution was extracted with 10% ether / hexane (8 x 15 mL) until no product remained in the aqueous layer. The ethereal layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated to yield 3 g (100%) of pure ketone **65**. R_f 0.58 (1:1 ether / hexane) ^1H NMR (250 MHz, CDCl_3) δ 7.54-7.07 (br m, 4H), 3.0 (t, 2H, $J = 7.5$ Hz), 2.77 (t, 2H, $J = 7.5$ Hz), 2.16 (s, 3H)



Side chain 66:

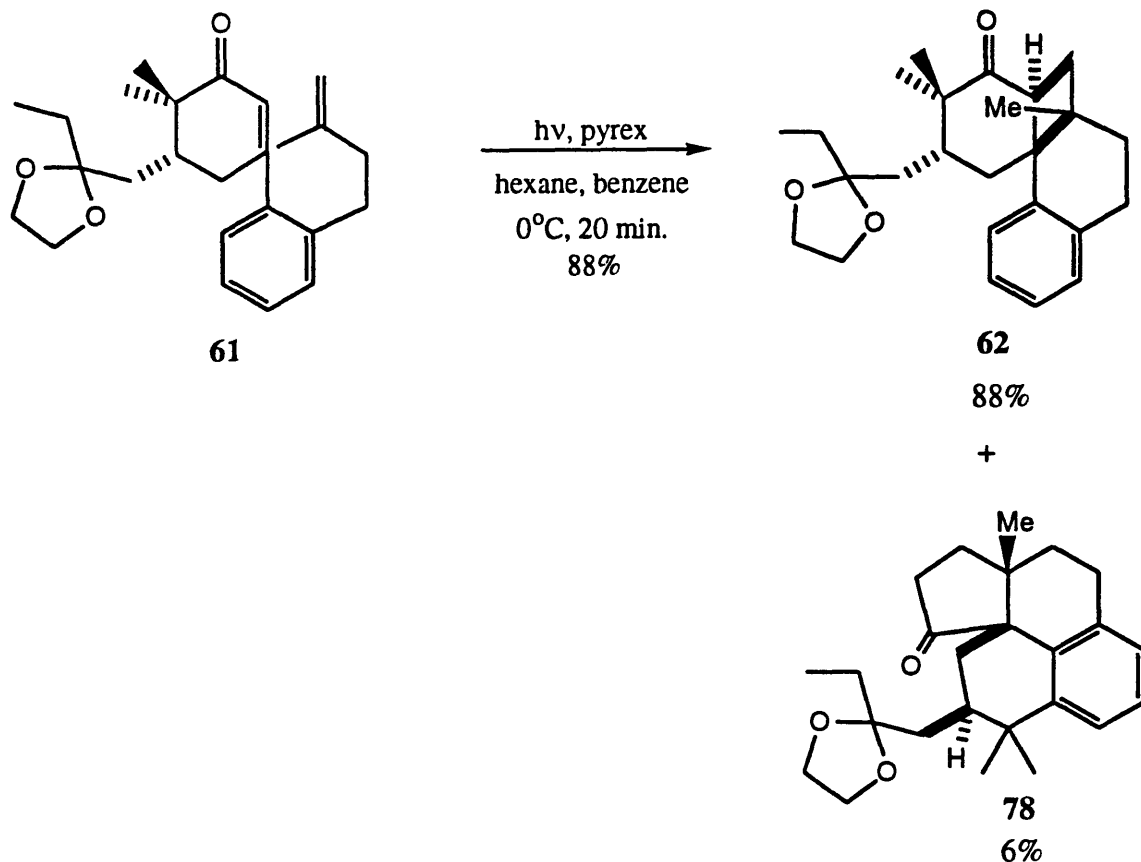
To a dry, 25 mL, round bottomed flask charged with argon were added methyltriphenylphosphonium bromide, (1.89 g, 5.28 mmol) and dry tetrahydrofuran (10 mL). The mixture was cooled to -78 °C and *n*-butyllithium was added dropwise which caused a color change to bright yellow. After addition, the Wittig reagent was warmed to 0 °C, and to it ketone **65** (1.0 g, 4.4 mmol) in 3 mL tetrahydrofuran was added via cannula. The reaction was then warmed to room temperature and stirred over night under argon. The mixture was filtered to remove the triphenylphosphine oxide byproduct, and saturated aqueous sodium bicarbonate solution was added. The tetrahydrofuran was then evaporated and the residue was diluted with ether. The layers were separated and the aqueous layer was washed with ether (3 x 5 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by column chromatography (1:4 ether / hexanes), and 0.84 g (85%) of a clear oil was isolated. R_f 0.74 (20% ether / hexane). ^1H NMR (300 MHz, CDCl_3) δ 7.54 (d, 1H, $J = 10.0$ Hz), 7.20-7.02 (m, 3H), 4.75 (d, 2H, $J = 15.0$ Hz), 2.88 (t, 2H, $J = 9.0$ Hz), 2.30 (t, 2H, $J = 9.0$ Hz), 1.82 (s, 3H)



Enone 61:

Thiophene (0.37 mL, 4.5 mmol) was dissolved in 0.4 mL dry ether under argon and the solution was cooled to -78 °C at which time *n*-butyllithium (1.7 mL, 4.4 mmol, 2.57 M in hexanes) was added dropwise and the solution was warmed to 0 °C, and was stirred for 1 h. The solution was then re-cooled to -78 °C and dry cuprous cyanide (0.40 g, 4.4 mmol) was added in one portion under a stream of argon. The heterogeneous mixture was warmed to room temperature for 20 minutes, and was then re-cooled to -78 °C. Separately, side chain **66** (1.0 g, 4.4 mmol) was dissolved in 3 mL ether under argon and was cooled to -78 °C. *tert*-Butyllithium (5.2 mL, 8.9 mmol, 1.74 M in pentane) was added dropwise, and the solution was stirred at this temperature for 45 min. The solution was then added, via cannula, to the 2-thienyl cuprate mixture at -78 °C followed by warming to 0 °C for 10 minutes and re-cooling to -78 °C. At this time, boron trifluoride dietherate (0.54 mL, 4.4 mmol) was added, followed by the addition of enol triflate **54** (1.1 g, 3.0 mmol), in 2 mL ether, via cannula. The reaction was stirred at -78 °C for 10 minutes followed by warming to -20 °C. The reaction was then quenched by the addition of saturated aqueous sodium bicarbonate solution. The layers were separated and the aqueous layer was washed (3 x 5 mL) with ether. The ethereal layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified via flash column

chromatography (SiO₂, 1% ether / dichloromethane) to yield 1.08 g (99%) pure photosubstrate **61**. *R_f* 0.55 (1:1 ether / hexanes). $[\alpha]^{20}_{\text{D}} +65.41$ (c=1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.22 (m, 2H), 7.20 (ddd, 1H, *J* = 2.0, 7.3, 7.3 Hz), 7.08 (dd, 1H, *J* = 7.3 Hz), 5.93 (d, 1H, *J* = 2.0 Hz), 4.71 (s, 1H), 4.76 (s, 1H), 4.98 - 3.83 (m, 4H), 2.92 (dd, 1H, *J* = 4.4, 19.5 Hz), 2.73 (m, 1H), 2.73 (ddd, 1H, *J* = 7.3, 10.3, 10.3 Hz), 2.52 (ddd, 1H, *J* = 2.0, 9.3, 19.5 Hz), 2.24 (t, 2H, *J* = 7.8 Hz), 2.15 (dddd, 1H, *J* = 1.5, 4.4, 9.3, 9.3 Hz), 1.91 (dd, 1H, *J* = 2.0, 14.7 Hz), 1.73 (s, 3H), 1.63 (pq, 2H, *J* = 7.3 Hz), 1.57 (dd, 1H, *J* = 9.3, 14.7 Hz), 1.23 (s, 3H), 1.06 (s, 3H), 0.89 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ 204.2, 160.8, 145.1, 140.5, 138.2, 129.4, 128.2, 127.1, 126.8, 126.0, 112.1, 110.4, 65.0, 64.5, 44.3, 39.7, 39.6, 36.3, 36.1, 31.8, 30.0, 22.5, 19.0, 8.1. FTIR (thin film, cm⁻¹) 2967, 2881, 1668, 1458, 1382, 1265, 1203, 1150, 1070, 947. HRMS calculated for C₂₅H₃₄O₃ (M⁺): 382.2508. Found: 382.2503.



Photocyclization of enone **61**:

Enone **61** (32 mg, 0.09 mmol), dissolved in ~1 mL ether, was added to a 250 mL Pyrex container equipped with a 450 Watt, medium pressure Conrad-Hanovia immersion lamp and triple walled Pyrex immersion well. The apparatus was pumped under vacuum for 15 minutes and hexanes (250 mL) and benzene (50 mL) was then added under argon. After the solution was degassed for 30 minutes, the reaction vessel was cooled to 0°C , and the substrate was irradiated for 20 minutes. The solution was concentrated *in vacuo*, and purified via flash column chromatography (SiO_2 , 20 % ether / hexane).

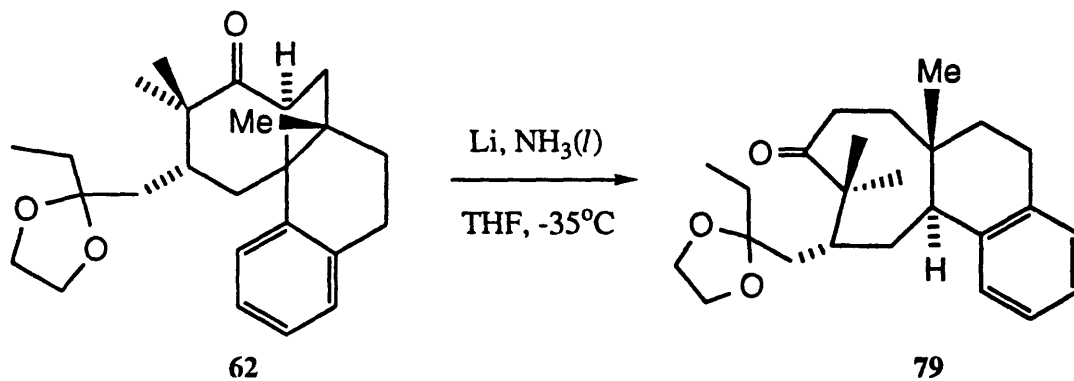
Desired cyclobutane photoproduct **62**:

Afforded 28 mg (88%) of pure product as a single diastereomer. R_f 0.61 (1:1 ether / hexanes). $[\alpha]_D^{20} +62.05$ ($c = 0.8$, CHCl_3). ^1H NMR (C_6D_6 , 500 MHz) δ 7.14 (d, 1H,

$J = 8.7$ Hz), 7.06 (t, 1H, $J = 8.7$ Hz), 6.96 (t, 1H, $J = 8.7$ Hz), 6.89 (d, 1H, $J = 8.7$ Hz), 3.49-3.37 (m, 4H), 3.09 (dd, 1H, $J = 9.7, 11.0$ Hz), 2.52 - 4.49 (m, 1H), 2.49 (ddd, 1H, $J = 6.5, 11.6, 17.4$ Hz), 2.37 (dd, 1H, $J = 3.9, 16.5$ Hz), 2.24 (ddd, 1H, $J = 3.9, 3.9, 17.4$ Hz), 1.96 (dd, 1H, $J = 9.7, 12.9$ Hz), 1.75 (dd, 1H, $J = 11.0, 12.9$ Hz), 1.77-1.68 (m, 2H), 1.64 (q, 1H, $J = 7.7$ Hz), 1.55 (q, 1H, $J = 7.7$ Hz), 1.48-1.42 (m, 2H), 1.31 (s, 3H), 1.23 (dd, 1H, $J = 9.7, 16.5$ Hz), 1.16 (s, 3H), 1.07 (s, 3H), 0.49 (t, 3H, $J = 7.7$ Hz); a COSY - 90 (C_6D_6 , 300 MHz) experiment was performed to determine coupling partners, and an NOE difference experiment (C_6D_6 , 500 MHz) was performed to determine stereochemistry. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 217.4, 138.1, 129.6, 128.3, 126.8, 125.5, 123.6, 112.0, 64.7, 64.3, 49.8, 48.3, 46.8, 45.5, 39.1, 39.1, 37.7, 35.5, 30.0, 26.9, 25.6, 22.4, 20.0, 15.2, 8.1. FTIR (thin film, cm^{-1}) 3499, 3062, 2970, 2937, 2880, 1688, 1600, 1494, 1454, 1434, 1382, 1336, 1265, 1236, 1211, 1145, 1114, 1072, 1047, 1006, 948. HRMS calculated for $C_{25}H_{34}O_3$ (M^+): 382.2508. Found: 382.2496.

Norrish type I side product 78:

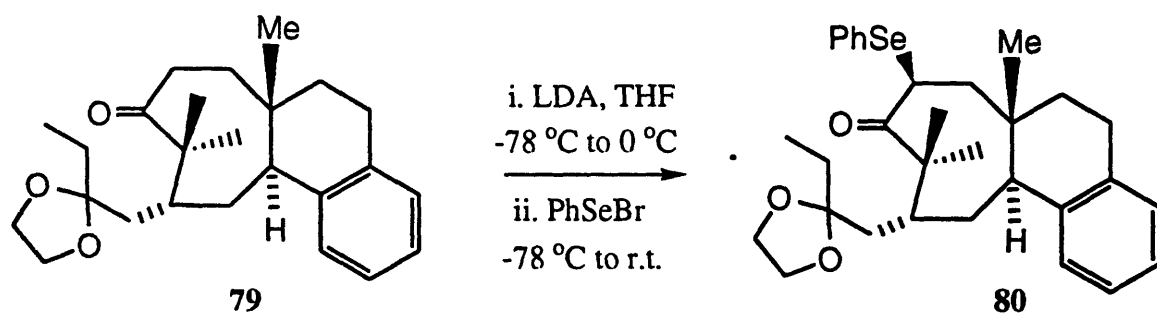
1.8 mg (6%) was obtained. R_f 0.58 (1:1 ether / hexane). 1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dddd, 1H, $J = 0.6, 0.6, 1.4, 7.9$ Hz), 7.13 (dd, 1H, $J = 7.4, 8.0$ Hz), 6.87 (dddd, 1H, $J = 1.1, 1.1, 1.1, 7.4$ Hz), 4.00 - 3.85 (m, 4H), 2.78 (dddd, 1H, $J = 0.8, 1.2, 6.1, 11.3, 17.0$ Hz), 2.67 (dddd, 1H, $J = 0.6, 0.6, 4.0, 6.4, 17.0$ Hz), 2.52 (dddd, 1H, $J = 0.6, 2.2, 10.8, 19.2$ Hz), 2.35 (ddd, 1H, $J = 8.9, 9.4, 19.2$ Hz), 2.15 (ddd, 1H, $J = 8.9, 10.9, 13.1$ Hz), 2.10 (dd, 1H, $J = 2.4, 13.5$ Hz), 1.91 (dddd, 1H, $J = 1.2, 2.6, 9.5, 12.7$ Hz), 1.88 (dd, 1H, $J = 1.2, 14.6$ Hz), 1.73 (ddd, 1H, $J = 2.2, 9.6, 12.9$ Hz), 1.72 (ddd, 1H, $J = 6.2, 11.2, 13.7$ Hz), 1.60 (pdq, 2H, $J = 7.3, 14.0$ Hz), 1.57 (m, 1H), 1.50 (ddd, 1H, $J = 3.9, 6.1, 13.7$ Hz), 1.39 (s, 3H), 1.37 (dd, 1H, $J = 9.5, 14.7$ Hz), 1.05 (s, 3H), 1.01 (s, 3H), 0.91 (t, 3H, $J = 7.5$ Hz).



Cyclooctanone 79:

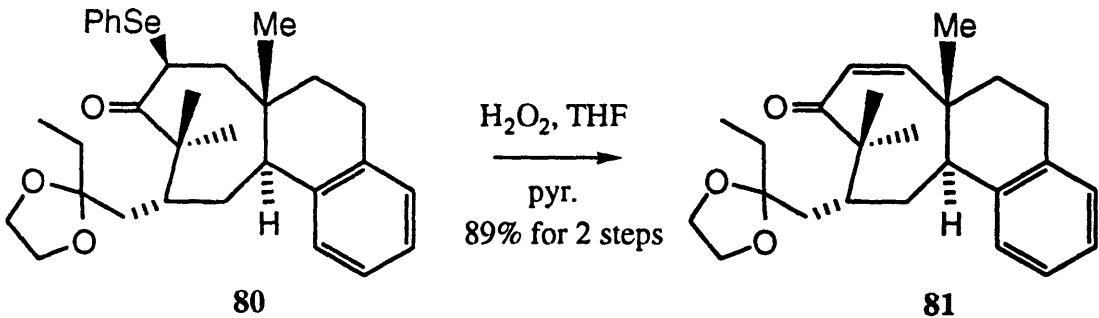
A dry, 25 mL, round-bottom flask, was cooled to -78 °C with a dry ice / acetone bath. The flask was evacuated with a vacuum pump, and into it, ammonia (~10 mL) was condensed. Calcium metal (8 mg, 0.2 mmol) was then added and the mixture was warmed to -35 °C. The reaction was stirred at this temperature until it turned deep blue and no calcium metal fragments were visible -- approximately 30 min. Cyclobutane photoproduct **62** (84 mg, 0.20 mmol), dissolved in 5 mL tetrahydrofuran, was transferred via cannula into the liquid ammonia solution, causing the reaction to turn clear. Quenching was performed by the careful addition of saturated ammonium chloride via pipette. The mixture was warmed to room temperature, and the ammonia and tetrahydrofuran were evaporated. The product was dissolved in ether, and the layers were separated. The aqueous layer was washed with ether (3 x 5 mL), and the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The product was purified via flash column chromatography (SiO₂, 25% ether / hexane) to yield 0.71 mg (85%) pure cyclooctanone **79**. R_f 0.19 (25% ether / hexane). ¹H NMR (500 MHz, C₆D₆) δ 7.23 (t, 1H, *J* = 7.8 Hz), 7.05 (dddd, 1H, *J* = 0.6, 1.7, 7.8, 7.8 Hz), 7.00 (dddd, 1H, *J* = 0.6, 1.4, 7.3, 7.3 Hz), 6.94 (d, 1H, *J* = 7.3 Hz), 3.48-3.39 (m, 4H), 2.98 (ddd, 1H, *J* = 2.9, 12.4, 12.2 Hz), 2.77 (dd, 1H, *J* = 2.9, 13.2 Hz), 2.68 (ddd, 1 H, *J* = 3.4, 12.7, 16.1 Hz), 2.57 (ddd, 1H, *J* = 5.4, 5.4, 11.7 Hz), 2.30 (ddd, 1H, *J* = 3.9, 3.9, 16.1 Hz), 2.09 (ddd, 1H, *J* = 4.4, 13.2, 17.6 Hz), 2.07

(ddd, 1H, $J = 3.9, 6.8, 12.2$ Hz), 1.95 - 1.88 (m, 1H), 1.84 (ddd, 1H, $J = 2.9, 2.9, 15.1$ Hz), 1.84 (dd, 1H, $J = 1.5, 14.7$ Hz), 1.54 (dq, 2H, $J = 7.8, 14.7$ Hz), 1.52 (ddd, 1H, $J = 3.4, 6.8, 13.2$ Hz), 1.29 (ddd, 1H, $J = 4.4, 11.7, 11.7$ Hz), 1.21 (s, 3H), 1.18 (dd, 1H, $J = 6.8, 15.1$ Hz), 1.17 (ddd, 1H, $J = 3.8, 3.8, 12.8$ Hz), 1.00 (s, 3H), 0.99 (s, 3H), 0.93 (t, 3H, $J = 7.5$ Hz); a COSY-90 experiment (CDCl_3 , 500 MHz) was performed to determine coupling partners, and an nOe difference experiment was performed to determine stereochemistry. ^{13}C NMR (CDCl_3 , 75 MHz) δ 220.6, 141.7, 137.7, 128.6, 128.2, 125.6, 124.8, 112.1, 64.8, 64.4, 50.4, 44.9, 42.4, 41.5, 41.0, 38.6, 37.7, 35.8, 33.5, 30.2, 26.5, 25.5, 19.8, 16.0, 8.3. FTIR (thin film, cm^{-1}) 3059, 2971, 2932, 2882, 2364, 2343, 2250, 1698, 1490, 1455, 1385, 1366, 1338, 1302, 1283, 1244, 1205, 1149, 1112, 1098, 1071, 1056, 998, 952, 920. HRMS calculated for $\text{C}_{25}\text{H}_{26}\text{O}_3$ (M^+): 384.26644. Found: 384.26681. Analysis calculated for $\text{C}_{25}\text{H}_{26}\text{O}_3$: C 78.08%; H 9.44%. Found: C 77.76%; H 9.40%.



α - Phenylselenenylketone 80:

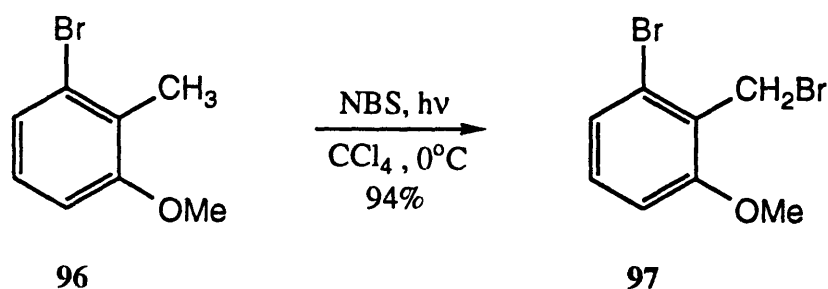
A solution of cyclooctanone **79** (0.25 g, 0.67 mmol) in 5 mL tetrahydrofuran, under argon, was cooled to $-78\text{ }^{\circ}\text{C}$, and to it was added lithium diisopropylamide (1.1 mmol, 1.5 equivalents) dropwise. The reaction was warmed to $0\text{ }^{\circ}\text{C}$ and was stirred for 1 h, at which time the reaction was recooled to $-78\text{ }^{\circ}\text{C}$. Phenylselenium bromide (in 1 mL tetrahydrofuran) was then added, via cannula, and the reaction was allowed to warm to room temperature. Quenching was performed by the addition of saturated aqueous sodium bicarbonate solution, and the tetrahydrofuran was evaporated. The layers were then separated, and the product was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated to afford a yellow oil that was carried on, without further purification, to the next step of forming the enone.



Enone 81:

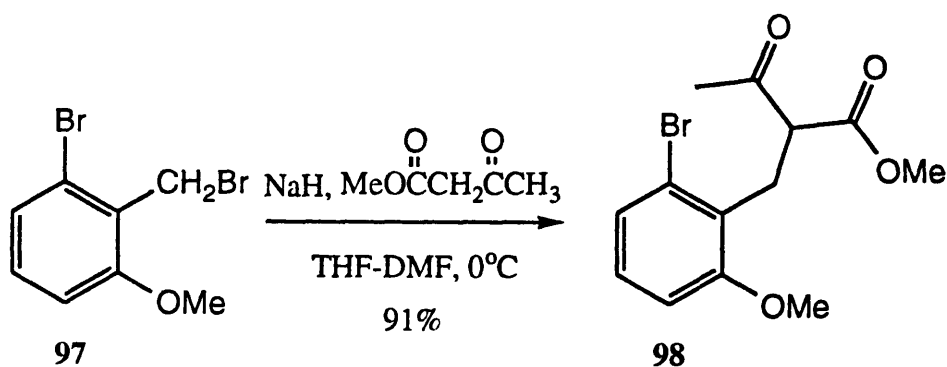
The crude mixture containing α -phenylselenenylketone **80**, formed in the previous step, was dissolved in 15 mL tetrahydrofuran and to this solution, 3 mL pyridine was added. Hydrogen peroxide (0.2 mL, 30% in water) was added, and the reaction was stirred at room temperature for 22 h, at which time saturated aqueous sodium bicarbonate solution was added and the tetrahydrofuran was evaporated. The resulting residue was diluted with dichloromethane, and the layers were separated. The aqueous layer was washed with dichloromethane, and the combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified via flash column chromatography (SiO₂, 1:2 ether / hexane) to yield 0.22 g (89%) enone **81**. R_f = 0.50 (1:1 ether / hexane). $[\alpha]_D^{20}$ +9.05 (c = 1.0). ¹H NMR (300 NMR, CDCl₃) δ 7.35 (d, 1H, J = 8.3 Hz), 7.2 - 7.0 (m, 3H), 5.78 (d, 1H, J = 13.2 Hz), 5.72 (d, 1H, J = 13.2 Hz), 4.0 - 3.8 (m, 4H, ketal), 2.91 (dd, 1H, J = 5.0, 14.3 Hz), 2.85 (dd, 1H, J = 7.7, 16.5 Hz), 2.68 - 2.52 (m, 2H), 2.07 (ddd, 1H, J = 4.5, 10.5, 10.5 Hz), 2.01 (dd, 1H, J = 5.0, 13.5 Hz), 1.90 (dd, 1H, J = 2.0, 15.0 Hz), 1.68 (pq, 2H, J = 7.3 Hz), 1.60 - 1.52 (m, 2H), 1.36 (dd, 1H, J = 7.7, 15.0 Hz), 1.15 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.92 (t, 3H, J = 7.3 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 215.2, 145.6, 139.1, 136.7, 128.8, 127.4, 126.0, 125.4, 121.2, 112.2, 64.9, 64.4, 51.0, 39.5, 38.9, 37.9, 37.7, 37.5, 36.1, 30.3, 26.9, 26.1, 18.3, 15.4, 8.3. FTIR (thin film, cm⁻¹) 2968, 2931, 2879, 2360, 1682, 1492, 1452, 1384, 1227, 1204, 1138, 1093, 1063, 952, 914. HRMS calculated for

$\text{C}_{25}\text{H}_{34}\text{O}_3$ (M^+): 382.25079. Found: 382.25025. Analysis calculated for $\text{C}_{25}\text{H}_{34}\text{O}_3$: C 78.48%; H 9.00%. Found: C 78.17%; H 9.27%.



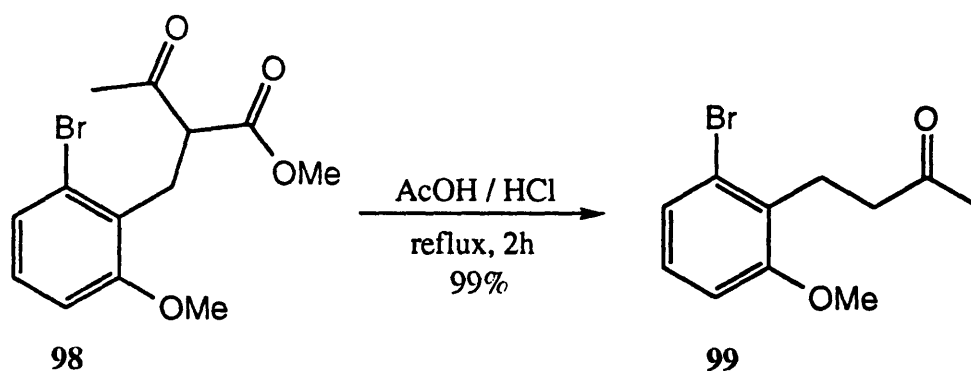
3-Bromo-2-bromomethylanisole 97:

To a suspension of *N*-bromosuccinimide (13.7 g, 77 mmol) and carbon tetrachloride (800 mL) was added 3-bromo-2-methylanisole **96** (14.1 g, 70 mmol) and the mixture was thoroughly purged with argon. The mixture was then irradiated at 0 °C with a sun lamp for 2.5 hours, at which time the reaction was filtered to remove the succinimide. The filtrate was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was recrystallized from hexane to yield 18.2 g (94%) pure 3-bromo-2-bromomethylanisole **97**. *R_f* 0.64 (1:1 ether / hexanes). m.p. = 101-103 °C. ¹H NMR (250 MHz, CDCl₃) δ 7.14 (m, 2H), 6.83 (dd, 1H, *J* = 1.8, 7.5 Hz), 4.74 (s, 2H), 3.94 (s, 3H, OMe). HRMS calculated for C₈H₈Br₂O (*M*⁺): 277.8942. Found: 277.8946.



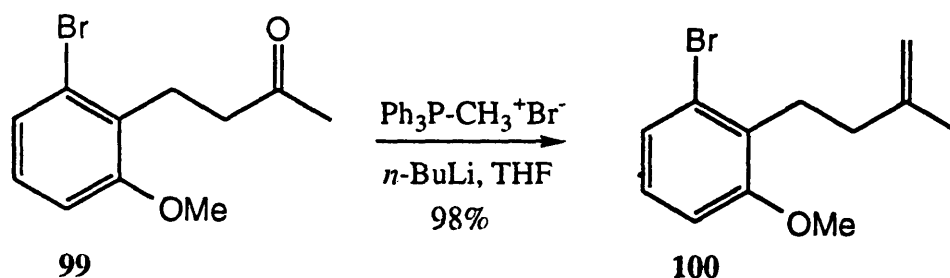
β-Ketoester **98**:

To a solution of methyl acetoacetate (3.3 g, 29 mmol) in 30 mL tetrahydrofuran and 30 mL *N,N*-dimethylformamide, at 0 °C, under argon was added via cannula a slurry of sodium hydride (0.69 g, 29 mmol) in tetrahydrofuran (5 mL). After deprotonation was completed, as evidenced by the cessation of hydrogen evolution, 3-bromo-2-bromomethylanisole **97** (5.3 g, 19 mmol) in 5 mL tetrahydrofuran was added via cannula, and the reaction was warmed to room temperature and stirred for 2 h. Quenching was then performed by the addition of 20 mL saturated aqueous sodium bicarbonate solution, and the tetrahydrofuran was evaporated *in vacuo*. The crude product was diluted with 100 mL water, and the aqueous layer was extracted with 5% ether / hexanes. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The product was purified by recrystallization (1:1 ether / hexane) to yield 5.6 g (91%) of pure β-ketoester **98**. m.p. = 75.5-76.0 °C. *R_f* 0.43 (1:1 ether / hexane). ¹H NMR (300 MHz, CDCl₃) δ 7.15 (dd, 1H, *J* = 1.1, 8.1 Hz), 7.06 (t, 1H, *J* = 8.1 Hz), 6.78 (d, 1H, *J* = 8.1 Hz), 3.81 - 3.76 (m, 1 H, COCH₂CO), 3.79 (s, 3H), 3.69 (s, 3H), 3.39 (d, 2H, *J* = 7.5 Hz), 2.19 (s, 3H), ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 158.5, 128.7, 126.5, 125.6, 125.5, 125.1, 109.4, 58.1, 55.7, 54.9, 52.4, 12.5. FTIR (thin film, cm⁻¹) 2950, 2838, 2358, 1718, 1589, 1571, 1464, 1434, 1258, 1263, 1218, 1034. Analysis calculated for C₁₃H₁₅BrO₄: C 49.54%; H 4.80%. Found: C 49.38%; H 4.89%.



Ketone 99:

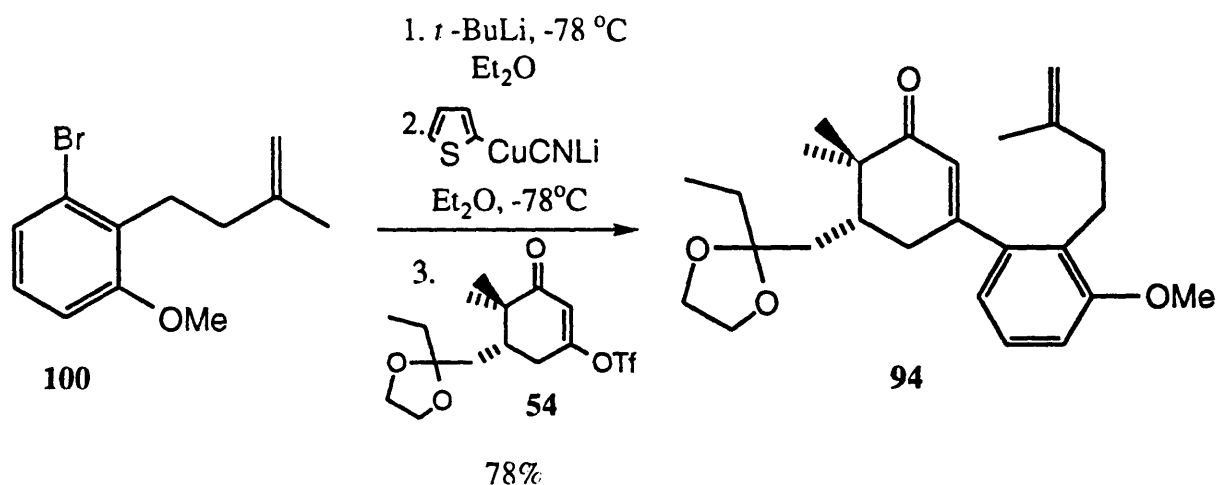
β -Ketoester **98** (5.6 g, 17.6 mmol) was added to a solution of 20 mL glacial acetic acid, 10 mL water, and 10 mL concentrated hydrochloric acid. The reaction was heated to reflux and stirred at that temperature for 1 h, at which time the reaction was cooled and the pH of the solution was neutralized by the addition of saturated aqueous sodium bicarbonate solution. The product was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (SiO₂, 1:3 ether / hexane) to yield 4.5 g (99%) of pure ketone **99**. *R_f* 0.58 (1:1 ether / hexane). m.p. = 59 - 60 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.14 (dd, 1H, *J* = 1.1, 8.2 Hz), 7.03 (t, 1H, *J* = 8.2 Hz), 6.78 (d, 1H, 8.2 Hz), 3.80 (s, 3H, OMe), 3.06 (t, 2H, *J* = 8.1 Hz), 2.63 (t, 2H, *J* = 8.1 Hz), 2.18 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.0, 158.0, 129.0, 128.1, 125.1, 124.9, 109.4, 55.8, 42.3, 29.7, 24.5. HRMS calculated for C₁₁H₁₃BrO₂ (M⁺): 256.0099; found: 256.0097.



Anisole side chain 100:

To a 200 mL round-bottomed flask charged with argon was added methyltriphenylphosphonium bromide (7.8 g, 22 mmol) and 100 mL of dry tetrahydrofuran. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$, *n*-butyllithium (8.2 mL, 21 mmol, 2.55 M in hexanes) was added dropwise, and the yellow mixture was stirred at this temperature for 10 min. The reaction was then warmed to $0\text{ }^{\circ}\text{C}$, was stirred for 15 minutes, and was recooled to $-78\text{ }^{\circ}\text{C}$. Ketone **99** (4.5 g, 18 mmol), dissolved in 5 mL tetrahydrofuran, was then added via cannula to the $-78\text{ }^{\circ}\text{C}$ solution of Wittig reagent; the mixture was warmed to room temperature, and was quenched by the addition of acetone until the yellow color disappeared. The reaction was concentrated and filtered through silica gel to remove the triphenylphosphine oxide byproduct, and the tetrahydrofuran and acetone were evaporated *in vacuo*. The product was purified via flash chromatography (SiO_2 , 12% ether / hexanes), to afford 4.38 g (98%) pure anisole side chain **100**. R_f 0.75 (1:1 ether / hexane). ^1H NMR (300 MHz, CDCl_3) δ 7.15 (d, 1H, $J = 8.1$ Hz), 7.02 (t, 1H, $J = 8.1$ Hz), 6.79 (d, 1H, $J = 8.1$ Hz), 4.75 (s, 2H, geminal olefinic H's), 3.82 (s, 3H, OMe), 2.93 (t, 2H, $J = 8.5$ Hz), 2.18 (t, 2H, $J = 8.5$ Hz), 1.82 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.3, 146.0, 130.6, 127.6, 125.3, 124.8, 109.8, 109.3, 55.7, 36.5, 28.6, 22.5. FTIR (thin film, cm^{-1}) 3072, 2965, 2938, 2834, 1648, 1588, 1571, 1462, 1432, 1373, 1316, 1258, 1203, 1178, 1163, 1038, 887. Analysis calculated for $\text{C}_{12}\text{H}_{15}\text{BrO}$: C, 56.49; H, 5.93. Found: C, 56.30; H, 6.01. HRMS calculated for

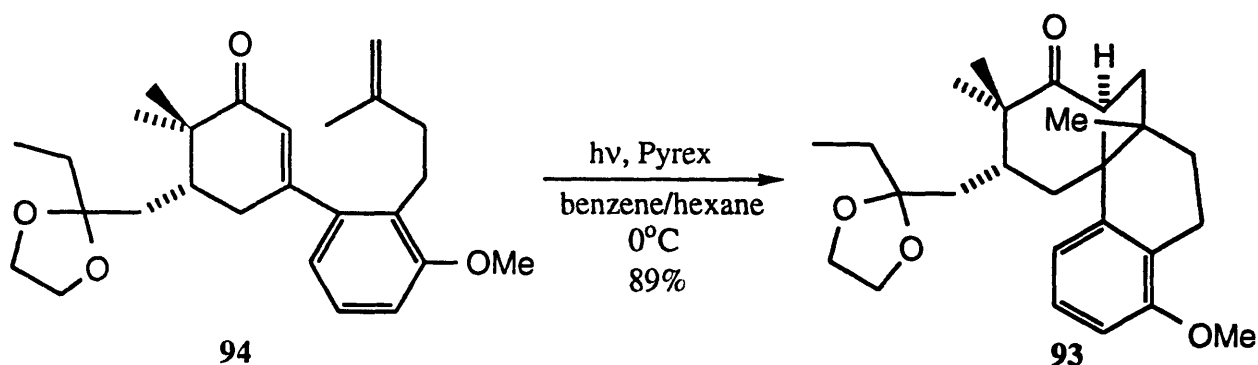
$\text{C}_{12}\text{H}_{15}\text{BrO}$ (M^+) 254.0306. Found: 254.0308. Analysis calculated for $\text{C}_{12}\text{H}_{15}\text{BrO}$: C 56.49%; H 5.95%. Found: C 56.30%; H 6.01%.



Enone 94:

Thiophene (1.6 mL, 20.0 mmol), dissolved in 35 mL dry ether under argon, was cooled to -78 °C, and *n*-butyllithium (14.9 mL, 19.4 mmol, 1.3 M in hexanes) was added dropwise. The solution was then warmed to 0 °C and was stirred for 1 h. The solution was then recooled to -78 °C and dry cuprous cyanide (1.7 g, 19.3 mmol) was added in one portion under a stream of argon. The heterogeneous green slurry was warmed to room temperature and stirred for 20 min., at which time the reaction formed a yellow-tan solution with a brown precipitate. The 2-thienyl cuprate solution was then recooled to -78 °C. Separately, anisole side chain **100** (4.9 g, 19.4 mmol), dissolved in 80 mL ether under argon, was cooled to -78 °C, and *t*-butyllithium (27.6 mL, 38.7 mmol, 1.4 M in pentane) was added dropwise. The yellow solution was stirred at this temperature for 15 minutes, at which time it was added, via cannula, to the 2-thienyl cuprate mixture at -78 °C, forming a brownish-red solution. The reaction was then warmed to 0 °C, forming a green solution, and was stirred for 15 minutes at which time the reaction turned yellow-tan. The cuprate solution was then recooled to -78 °C, and boron trifluoride dietherate (2.8 g, 2.4 mL, 19.4 mmol) was added in one portion. Enol triflate **54** (5.0 g, 12.9 mmol) in 10 mL ether was then added via cannula, and the reaction, which initially formed a dark red solution and

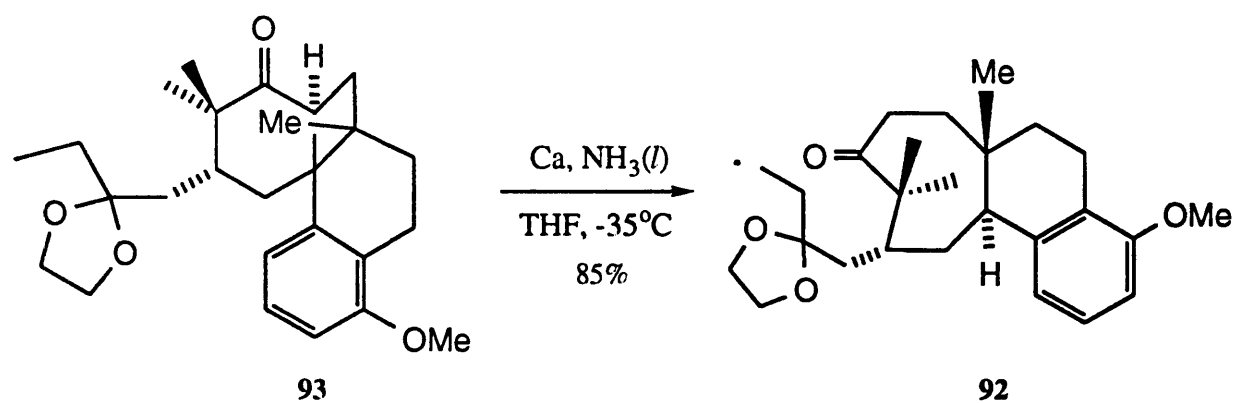
quickly turned yellow-tan with a brown precipitate, was stirred at -78 °C for 10 minutes followed by warming to -20 °C. The reaction was quenched by the addition of 50 mL saturated aqueous sodium bicarbonate solution at which time the reaction formed a dark brown slurry. The layers were separated and the aqueous layer was washed (6 x 25 mL) with ether. The ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to form a green oil. The crude product was separated by flash column chromatography on silica gel (1% ether / dichloromethane) to yield 4.15 g (78%) pure enone **94**. R_f 0.45 (1:1 ether / hexane). $[\alpha]_D^{20} +53.98$ ($c = 1.2$, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz) δ 7.17 (t, 1H, $J = 8.3$ Hz), 6.81 (d, 1H, $J = 8.3$ Hz), 6.67 (dd, 1H, $J = 1.0, 8.3$ Hz), 5.89 (d, 1H, $J = 1.5$ Hz), 4.68 (s, 1H), 4.65 (s, 1H), 3.98 - 3.85 (m, 4H), 3.82 (s, 3H, OMe), 2.89 (dd, 1H, $J = 4.9, 19.5$ Hz), 2.73 (ddd, 1H, $J = 5.9, 11.2, 12.7$ Hz), 2.64 (ddd, 1H, $J = 5.9, 10.8, 12.7$ Hz), 2.50 (ddd, 1H, $J = 2.0, 9.3, 19.5$ Hz), 2.19 (ddd, 1H, $J = 5.4, 14.7, 14.7$ Hz), 2.14 (dddd, 1H, $J = 1.5, 4.9, 9.3, 14.2$ Hz), 1.90 (dd, 1H, $J = 2.0, 14.7$ Hz), 1.73 (s, 3H), 1.63 (pq, 2H, $J = 7.3$ Hz), 1.56 (dd, 1H, $J = 9.8, 14.7$ Hz), 1.21 (s, 3H), 1.02 (s, 3H), 0.90 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 204.3, 160.8, 157.6, 146.0, 142.0, 127.0, 126.8, 126.7, 119.2, 112.0, 109.8, 109.7, 65.0, 64.5, 55.5, 44.3, 39.6, 38.2, 36.6, 36.0, 29.9, 26.5, 22.5, 22.5, 19.0, 8.1. FTIR (thin film, cm^{-1}) 3854, 3750, 3676, 3649, 3069, 2967, 2935, 2880, 2363, 1668, 1576, 1456, 1437, 1381, 1261, 1198, 1150, 1098, 1069, 947. HRMS calculated for $\text{C}_{26}\text{H}_{36}\text{O}_4$ (M^+): 412.2614. Found: 412.2615. Analysis calculated for $\text{C}_{26}\text{H}_{36}\text{O}_4$: C 75.62%; H 8.80%. Found: C 75.06%; H 8.63%.



Cyclobutane 93:

Enone **94** (1.00 g, 2.42 mmol), dissolved in ~3 mL ether, was added to 250 mL Pyrex reaction vessel equipped with a 450 Watt, medium pressure Conrad-Hanovia immersion lamp and triple-walled Pyrex immersion well. The apparatus was evacuated for 15 minutes and a mixture of hexanes (250 mL) and benzene (25 mL) was added under argon. After the solution was degassed for 30 minutes with a vigorous stream of argon, the enone **94** was irradiated with stirring and a vigorous stream of argon for 30 minutes. The solution was concentrated *in vacuo* to yield approximately 0.95 g of crude cyclobutane **93**. The product was purified by column chromatography (25% ether / hexane) to yield 0.89 g (89%) pure cyclobutane **93** in only one isomeric form. R_f 0.45 (1:1 ether / hexane). $[\alpha]_D^{20} +68.7$ ($c = 1$, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz) δ 7.12 (t, 1H, $J = 7.8$ Hz), 6.64 (t, 2H, $J = 7.8$ Hz), 3.94 - 3.79 (m, 4H), 3.81 (s, 3H, OMe), 2.99 (dd, 1H, $J = 9.8, 9.8$ Hz), 2.90 (ddd, 1H, $J = 3.7, 3.7, 16.6$ Hz), 2.54 (ddd, 1H, $J = 3.7, 9.8, 12.7$ Hz), 2.33 (dd, 1H, $J = 3.4, 14.6$ Hz), 2.32 (ddd, 1H, $J = 3.7, 12.7, 16.6$ Hz), 2.10 - 2.00 (m, 1H), 2.04 (dd, 1H, $J = 9.8, 10.4$ Hz), 1.84 (d, 1H, $J = 14.6$ Hz), 1.81 (ddd, 1H, $J = 3.7, 3.7, 12.9$ Hz), 1.74 (q, 1H, $J = 7.3$ Hz), 1.71 (m, 1H), 1.67 (q, 1H, $J = 7.3$ Hz), 1.70-1.65 (m, 1H), 1.39 (dd, 1H, $J = 9.8, 14.6$ Hz), 1.29 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 0.92 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (CDCl_3 , 60 MHz) δ 217.2, 155.9, 146.8, 127.0, 126.8, 119.0, 111.8, 106.7, 64.3, 64.1, 55.3, 48.1, 46.6, 45.2, 38.4,

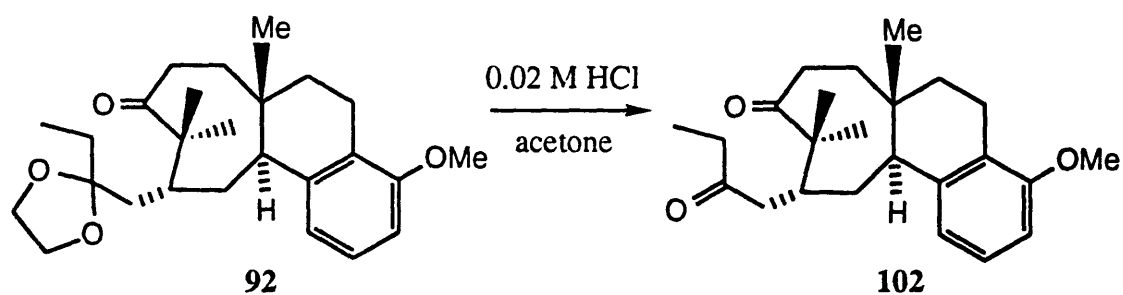
37.9, 37.5, 37.4, 35.2, 29.8, 25.7, 22.0, 19.9, 18.7, 8.1. FTIR (thin film, cm^{-1}) 3065, 2967, 2938, 2880, 2835, 2249, 1686, 1581, 1461, 1438, 1380, 1360, 1338, 1262, 1246, 1203, 1130, 1104, 1087, 1071, 1047, 1005, 948, 918, 866, 827. HRMS calculated for $\text{C}_{26}\text{H}_{36}\text{O}_4$ (M^+): 412.2614. Found: 412.2616



Cyclooctanone **92**:

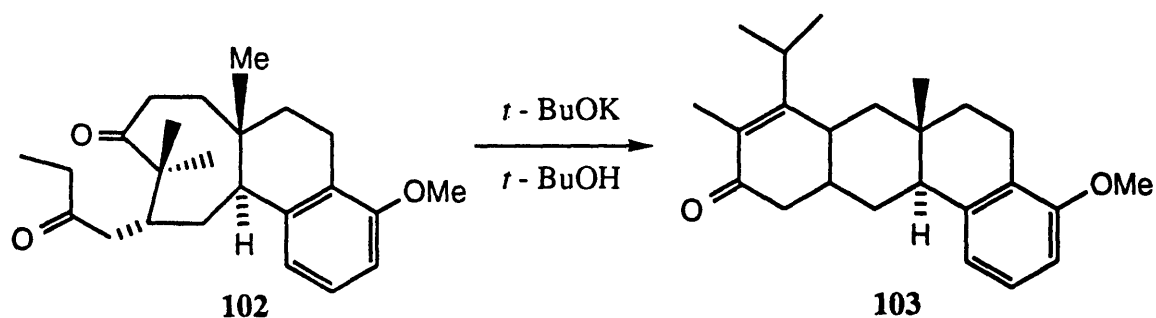
A dry, 25 mL flask, was cooled to -78°C with a dry ice / acetone bath. The flask was evacuated with a vacuum pump, and into it ammonia (~ 10 mL) was condensed. Calcium metal (8.0 mg, 0.20 mmol, thoroughly scraped of any calcium oxide) was added and the mixture was warmed to -35°C . The reaction was stirred at this temperature until it turned deep blue and no calcium metal was visible -- approximately 30 minutes. Cyclobutane **93** (84 mg, 0.20 mmol), dissolved in 5 mL tetrahydrofuran, was added via cannula to the liquid ammonia solution, and the reaction immediately turned clear. The reaction was then quenched by the careful addition of saturated aqueous ammonium chloride via pipette. The mixture was warmed to room temperature and the ammonia and tetrahydrofuran were evaporated. The residue was diluted with ether and the layers were separated. The aqueous layer was washed with ether (3 x 5 mL), and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a mixture of cyclooctanone **92** and the corresponding alcohol, which was a product of over-reduction. This mixture was dissolved in 4 mL dichloromethane, and pyridinium chlorochromate on neutral alumina (110 mg, 1 mmol / g) was added followed by 0.2 mL pyridine. The reaction was stirred overnight at room temperature, after which time the slurry was filtered through a silica gel (SiO_2) / anhydrous magnesium sulfate plug. The solvent was then

evaporated, and the crude mixture was purified via flash column chromatography (SiO₂, 25% ether / hexane) 71 mg (85%) pure cyclooctanone **92**. *R_f* 0.19 (25% ether / hexane). ¹H NMR (CDCl₃, 500 MHz) δ 7.05 (t, 1H, *J* = 8.1 Hz), 6.74 (d, 1H, *J* = 7.8 Hz), 6.58 (d, 1H, *J* = 7.8 Hz), 4.00 - 3.75 (m, 4H), 3.74 (s, 3H, OMe), 3.20 (ddd, 1H, *J* = 3.8, 12.1, 12.1 Hz), 2.73 (ddd, 1H, *J* = 3.6, 3.6, 17.0 Hz), 2.60 (dddd, 1H, *J* = 1.7, 4.5, 7.0, 12.3 Hz), 2.53 (dd, 1H, *J* = 3.4, 12.8 Hz), 2.44 (ddd, 1H, *J* = 4.5, 13.0, 17.0 Hz), 2.16 (ddd, 1H, *J* = 3.8, 6.8, 12.8 Hz), 1.91 (dd, 1H, *J* = 1.7, 14.9 Hz), 1.89 (ddd, 1H, *J* = 4.5, 13.0, 15.3 Hz), 1.83 (m, 1H), 1.80 (ddd, 1H, *J* = 3.8, 6.8, 14.0 Hz), 1.71 (ddd, 1H, *J* = 3.4, 12.3, 12.9 Hz), 1.63 (q, 1H, *J* = 7.7 Hz), 1.62 (q, 1H, *J* = 7.7 Hz), 1.48 (ddd, 1H, *J* = 2.9, 4.4, 12.9 Hz), 1.39 (ddd, 1H, *J* = 4.3, 12.9, 12.9 Hz), 1.29 (dd, 1H, *J* = 7.2, 14.9 Hz), 1.10 (s, 6H), 1.08 (s, 3H), 0.88 (t, 3H, *J* = 7.65 Hz), COSY-90 (CDCl₃, 500 MHz) was run to determine coupling partners. ¹³C NMR (CDCl₃, 60 MHz) δ 220.6, 156.3, 143.1, 126.5, 125.7, 121.2, 112.1, 106.1, 64.9, 64.5, 55.3, 50.4, 44.9, 42.6, 41.6, 40.3, 38.6, 37.7, 35.2, 33.6, 30.2, 25.6, 19.4, 16.1, 8.3, 1.0. FTIR (thin film, cm⁻¹) 2968, 2933, 2361, 1696, 1652, 1584, 1558, 1540, 1507, 1464, 1386, 1339, 1256, 1213, 1081, 949. HRMS calculated for C₂₆H₃₈O₄ (M⁺): 414.27701. Found: 414.27716.



Diketone 102:

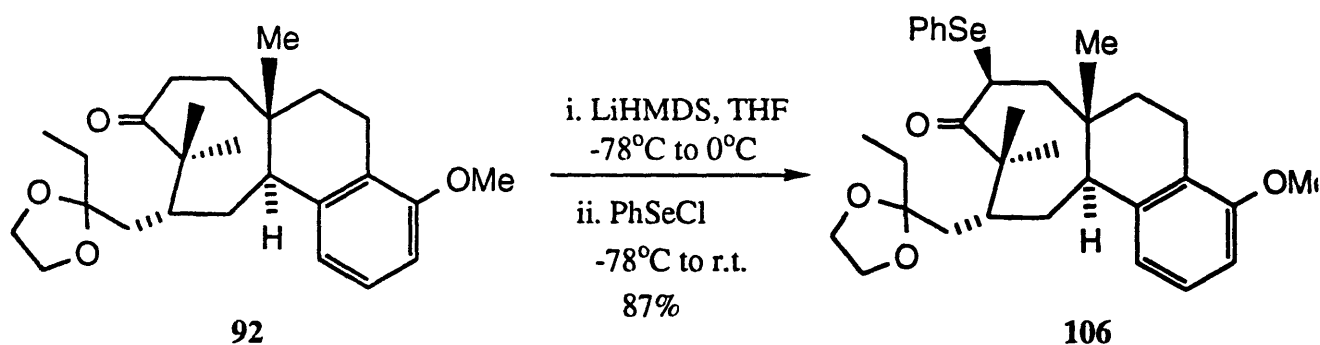
To a solution of cyclooctanone **92** (11 mg, 0.026 mmol) in 2 mL acetone was added 10% hydrochloric acid (1 μ L). The reaction was stirred at room temperature for 14 h, at which time saturated aqueous sodium bicarbonate solution was added, and the acetone was evaporated. The residue was diluted with ether, and the layers were separated. The aqueous layer was then washed with ether, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to yield 9.1 mg (96%) pure diketone **102**. R_f 0.19 (25% ether / hexane). ^1H NMR (300 MHz, CDCl_3) δ 7.05 (t, 1H, $J = 8.3$ Hz), 6.69 (d, 1H, $J = 8.3$ Hz), 6.58 (d, 1H, $J = 8.3$ Hz), 3.79 (s, 3H, OMe), 3.29 (dd, 1H, $J = 7.5, 14.5$ Hz), 3.24 (dddd, 1H, $J = 1.0, 3.5, 7.5, 14.5$ Hz), 2.72 (ddd, 1H, $J = 4.0, 4.0, 17.1$ Hz), 2.59 (dd, 1H, $J = 4.0, 17.5$ Hz), 2.55 - 2.30 (m, 3H), 2.47 (dd, 1H, $J = 7.3, 17.5$ Hz), 2.34 (dd, 1H, $J = 7.3, 17.5$ Hz), 2.23 - 2.13 (m, 1H), 2.19 (dd, 1H, $J = 9.5, 18.0$ Hz), 1.39 (d, 1H, $J = 5.5$ Hz), 3.35 (dd, 1H, $J = 4.0, 5.5$ Hz), 1.61 (dd, 1H, $J = 4.0, 12.0$ Hz), 1.48 (ddd, 1H, $J = 5.0, 13.0, 18.0$ Hz), 1.37 (ddd, 1H, $J = 5.0, 13.0, 13.0$ Hz), 1.19 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H), 1.02 (t, 3H, $J = 7.3$ Hz).



***trans* -Tetracycle 103**

To a solution of diketone **102** (48 mg, 0.13 mmol) in 3 mL tetrahydrofuran, under argon, at 0 °C, was added potassium *tert*-butoxide (200 mg, 1.8 mmol) in one portion. The reaction was warmed to room temperature and was stirred for 1.25 h at which time the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution. Following the removal of the tetrahydrofuran *in vacuo*, the aqueous layer was washed with ether, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The resulting oil was purified via flash column chromatography (SiO₂, 20 % ether / hexane) to yield 24 mg (49%) *trans*-tetracycle **103** as an inseparable mixture of 2 isomers. *R*_f 0.69 (1:1 ether / hexane). 9 mg (19%) of starting material was recovered. *R*_f 0.48 (1:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.13 (t, 1H, *J* = 7.8 Hz), 6.83 (d, 1H, *J* = 7.8 Hz), 6.71 (d, 1H, *J* = 7.8 Hz), 3.81 (s, 3H, OMe), 2.97 (sept., 1H, *J* = 7.1 Hz), 2.82 (dd, 1H, *J* = 7.5, 18.7 Hz), 2.79 - 2.65 (m, 2H), 2.59 (dd, 1H, *J* = 12.8, 18.2 Hz), 2.47 (dd, 1H, *J* = 3.2, 15.2 Hz), 2.25 (ddd, 1H, *J* = 5.7, 10.6, 14.8 Hz), 2.18 (dd, 1H, *J* = 2.7, 13.4 Hz), 2.09 (ddd, 1H, *J* = 2.7, 2.7, 13.4 Hz), 1.84 (d, 1.5 H, *J* = 2.0 Hz Me of one isomer), 1.82 (s, 1.5 H, Me of other isomer), 1.75 (ddd, 1H, *J* = 5.7, 13.2, 13.2 Hz), 1.68 - 1.53 (m, 2H), 1.23 (pd, 3H, *J* = 7.1 Hz, isopropyl Me's of one isomer), 1.15 (pd, 3H, *J* = 7.1 Hz, isopropyl Me's of other isomer), 0.85 (s, 1.5 H, Me of one isomer), 0.84 (s, 1.5H, Me of other isomer). FTIR

(thin film, cm^{-1}) 2924, 2856, 2349, 1665, 1581, 1462, 1434, 1379, 1320, 1258, 1084, 1053.



Phenylselenenylcyclooctanone 106:

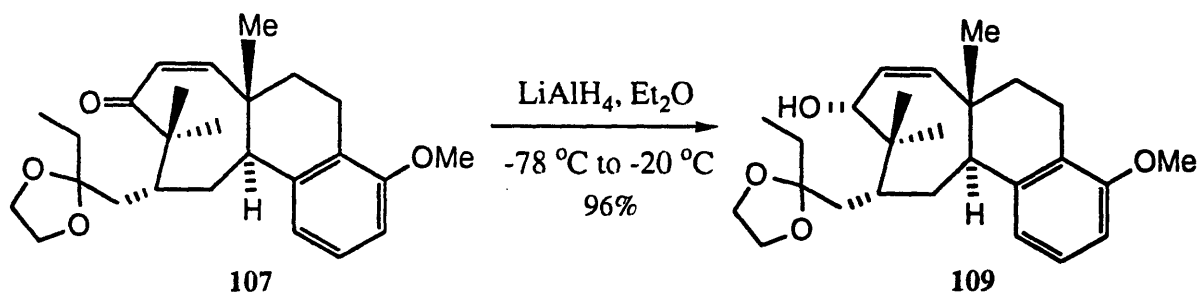
Cyclooctanone **92** (76 mg, 0.18 mmol) was placed in a dry, 25 mL, flask under argon, 4 mL dry tetrahydrofuran was added, and the solution was cooled to -78°C . Lithium bis(trimethylsilyl)amide (0.22 mL, 0.22 mmol, 1.0 M in tetrahydrofuran) was then added dropwise, the reaction mixture was warmed to 0°C , and was stirred at this temperature for 1 h. The reaction was then recooled to -78°C , phenylselenium chloride (42 mg, 0.22 mmol) dissolved in 2 mL tetrahydrofuran was added via cannula, and the reaction was allowed to warm to room temperature. Quenching was performed by the addition of 2 mL saturated aqueous sodium bicarbonate solution, the layers were separated, and the aqueous layer was washed (3 x 3 mL) with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and were concentrated *in vacuo*. The crude product was purified by recrystallization from ether to yield 88.2 mg (87%) white crystals. R_f 0.20 (25% ether / hexane). ^1H NMR (300 MHz, CDCl_3) δ 7.61 - 7.51 (m, 2H, SePh), 7.35 - 7.26 (m, 3H, SePh), 7.10 (t, 1H, $J = 7.8$ Hz), 7.02 (d, 1H, $J = 7.8$ Hz), 6.66 (d, 1H, $J = 7.8$ Hz), 4.19 (dd, 1H, $J = 5.4, 15.0$ Hz), 4.08 - 3.90 (m, 4H, ketal), 3.79 (s, 3H, OMe), 2.94 (t, 1H, $J = 15.0$ Hz), 2.88 - 2.80 (m, 1H), 2.73 (ddd, 1H, $J = 2.0, 8.0, 18.7$ Hz), 2.64 (dd, 1H, $J = 6.4, 11.8$ Hz), 2.54 (dd, 1H, $J = 5.9, 10.2$ Hz), 2.20 - 1.95 (m, 5H), 1.90 (ddd, 1H, $J = 5.9, 11.8, 11.8$ Hz), 1.70 (pdq, 2H, $J = 7.3, 15.1$ Hz), 1.46 (s, 3H), 1.42 (dd, 1H, $J = 8.0, 15.0$ Hz), 1.34 (ddd, 1H, $J = 2.0, 5.9,$

11.8 Hz), 1.03 (s, 3H), 0.96 (t, 3H, $J = 7.3$ Hz), 0.87 (s, 3H). Analysis calculated for $C_{32}H_{42}O_4Se$: C 67.34%; H 7.42%. Found: C 67.09%; H 7.33%.



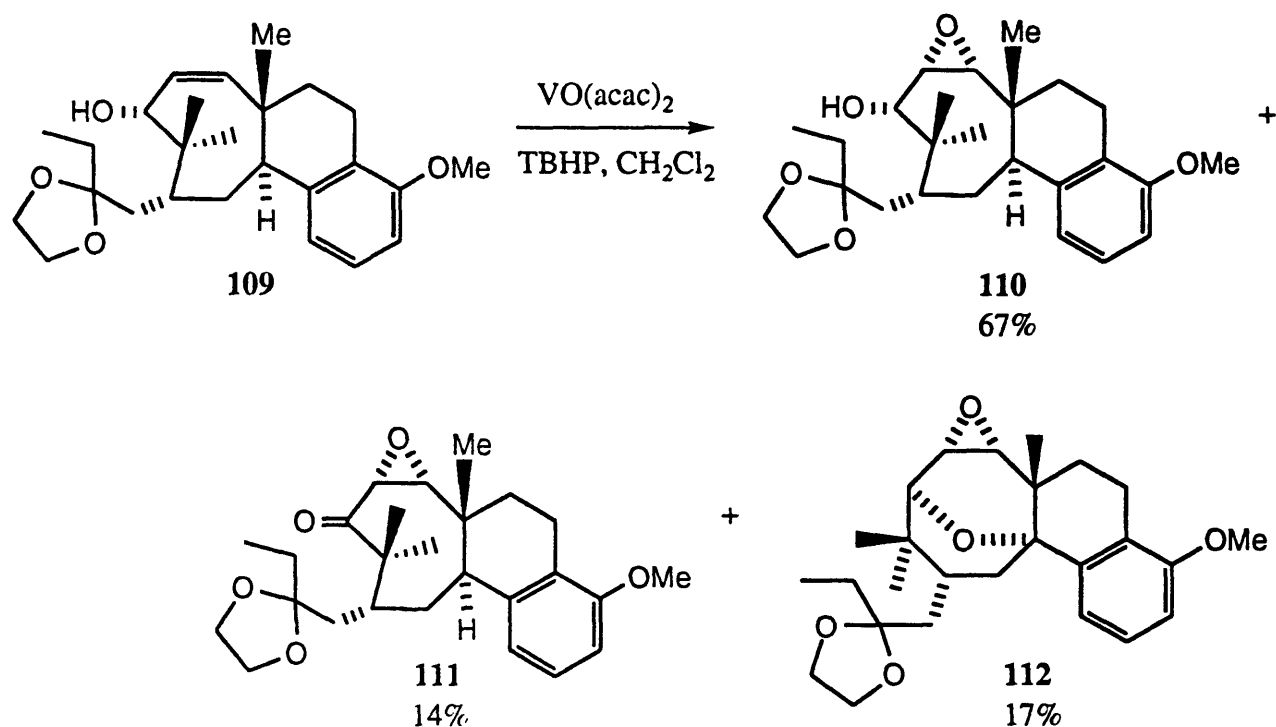
155

1258, 1220, 1146, 1083, 1062, 948, 909. NOE difference studies were also performed on the molecule to determine the stereochemistry of the olefinic bond. HRMS calculated for $C_{26}H_{36}O_4$ (M^+): 412.26136. Found: 412.26078.



Cyclooctenol 109:

A solution of enone **107** (30 mg, 0.07 mmol) in 1.5 mL dry ether was cooled to $-78\text{ }^{\circ}\text{C}$, and to it was added lithium aluminum hydride (0.10 mL, 1.0 M in ether). The solution was warmed to $-20\text{ }^{\circ}\text{C}$ and was stirred for 10 minutes at which time, the reaction was quenched by the addition of ethyl acetate followed by the addition of saturated aqueous sodium bicarbonate solution. The layers were then separated, and the product was extracted from the aqueous layer with ether. The combined ethereal extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified via flash column chromatography (SiO_2 , 30% ether / hexane) to afford 29 mg (96%) pure cyclooctenol **109**. R_f 0.40 (1:1 ether / hexane). $[\alpha]_{\text{D}}^{20} +23.85$ ($c = 1.5$, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.16 - 7.10 (m, 2H), 6.66 - 6.64 (m, 1H), 5.63 (d, 1H, $J = 13.5$ Hz), 5.52 (dd, 1H, $J = 7.0, 13.5$ Hz), 4.08 (d, 1H, $J = 7.0$ Hz), 3.95 - 3.80 (m, 1H), 3.80 (s, 3H, OMe), 2.79 (dd, 1H, $J = 6.5, 13.0, 18.0$ Hz), 2.24 (ddd, 1H, $J = 5.5, 14.0, 14.0$ Hz), 2.12 - 2.02 (m, 1H), 1.84 (d, 1H, $J = 12.5$ Hz), 1.76 (t, 1H, $J = 12.5$ Hz), 1.70 - 1.24 (m, 3H), 1.45 - 1.24 (m, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.87 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3) δ 156.6, 148.4, 145.1, 144.0, 125.8, 124.6, 119.3, 112.6, 106.0, 67.8, 64.7, 64.4, 55.3, 55.2, 54.9, 40.9, 39.7, 38.4, 37.4, 37.3, 36.7, 30.4, 29.2, 20.6, 18.0, 8.2. FTIR (thin film, cm^{-1}) 3483, 2964, 2935, 2878, 1580, 1456, 1435, 1373, 1339, 1301, 1260, 1157, 1138, 1085, 1069, 951, 922. HRMS calculated for $\text{C}_{26}\text{H}_{38}\text{O}_4$ (M^+): 414.27701. Found: 414.27716.



Vanadyl acetylacetonate epoxidation of cyclooctenol **109**:

To a 0 °C solution of cyclooctenol **109** (39 mg, 0.094 mmol) in 2 mL dichloromethane, under argon, was added *tert*-butyl hydroperoxide (0.5 mL, 5 - 6 M in decane) and vanadyl acetylacetonate (2.5 mg, 0.01 mmol). The dark red reaction was stirred at 0 °C for 9 h, during which time the reaction turned light yellow. The reaction was then quenched by the addition of saturated aqueous sodium bicarbonate solution, the layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated, and purified via flash column chromatography (SiO_2 , 1:1 ether / hexane).

Epoxy cyclooctanol **110**:

(27 mg, 67% -- isolated as a single diastereomer). R_f 0.27 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.09 (t, 1H, $J = 7.8$ Hz), 7.00 (d, 1H, $J = 7.8$ Hz), 6.62 (d, 1H, $J =$

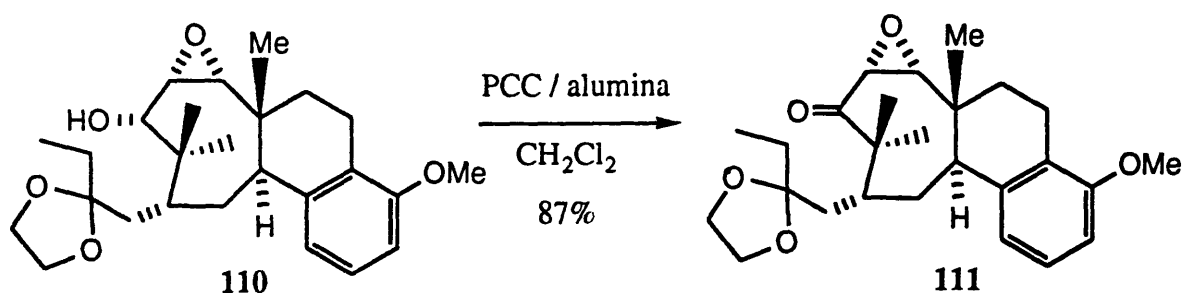
7.8 Hz), 4.16 (d, 1H, $J = 4.9$ Hz, carbinol H), 3.92 - 3.82 (m, 4H, ketal), 3.80 (s, 3H, OMe), 3.32 (dd, 1H, $J = 4.9, 4.9$ Hz), 2.99 (d, 1H, $J = 4.9$ Hz), 2.84 (ddd, 1H, $J = 2.0, 4.9, 18.1$ Hz), 2.57 (ddd, 1H, $J = 6.4, 13.2, 18.1$ Hz), 2.20 - 2.04 (m, 3H), 1.84 (d, 1H, $J = 15.9$ Hz), 1.81 (ddd, 1H, $J = 5.9, 13.2, 13.2$ Hz), 1.75 (ddd, 1H, $J = 2.0, 5.9, 13.2$ Hz), 1.65 (pq, 2H, $J = 7.3$ Hz), 1.70 - 1.50 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H), 0.88 (t, 3H, $J = 7.3$ Hz), 0.88 (s, 3H). FTIR (thin film, cm^{-1}) 3479, 3125, 2963, 2925, 1727, 1574, 1464, 1436, 1378, 1364, 1307, 1254, 1197, 1083, 1063, 942. FTIR (thin film, cm^{-1}) 3479, 2963, 2925, 1727, 1574, 1464, 1436, 1384, 1307, 1254, 1197, 1083, 1063.

Epoxy cyclooctanone 111:

(5.7 mg, 14 % as a single diastereomer) R_f 0.15 (1:1 ether / hexane). For spectral data for next compound.

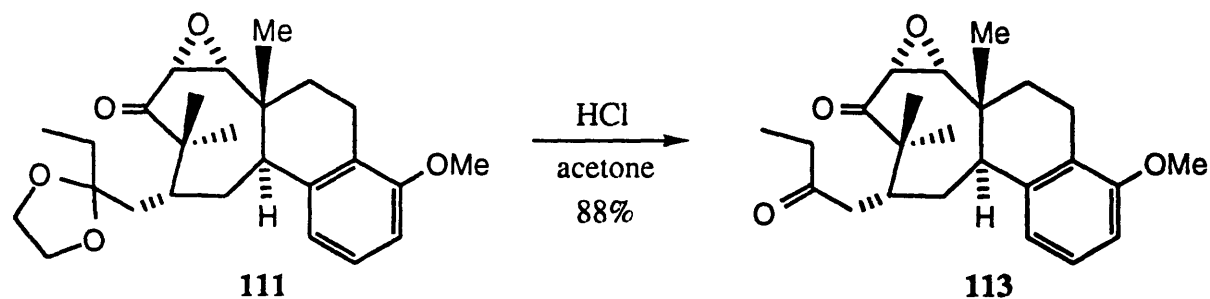
Cyclic Ether 112:

(6.8 mg, 17% as a single diastereomer) R_f 0.19 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.30 (d, 1H, $J = 8.3$ Hz), 7.18 (dd, 1H, $J = 7.8, 8.3$ Hz), 6.69 (d, 1H, $J = 7.8$ Hz), 3.92 - 3.85 (m, 4H, ketal), 3.80 (s, 3H, OMe), 3.73 (s, 1H), 3.34 (dd, 1H, $J = 1.0, 3.9$ Hz), 3.07 (d, 1H, $J = 3.9$ Hz), 2.85 (ddd, 1H, $J = 2.4, 4.4, 17.6$ Hz), 2.44 (ddd, 1H, $J = 4.4, 13.7, 17.6$ Hz), 2.07 (dd, 1H, $J = 4.4, 13.7$ Hz), 2.05 - 2.00 (m, 1H), 1.99 (d, 1H, $J = 2.0, 13.7$ Hz), 1.88 - 1.84 (m, 1H), 1.82 (dd, 1H, $J = 1.0, 14.8$ Hz), 1.62 (pq, 2H, $J = 7.3$ Hz), 1.65 - 1.58 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 0.86 (t, 3H, $J = 7.3$ Hz), 0.85 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.2, 141.7, 126.7, 126.3, 121.3, 112.1, 107.9, 74.1, 73.4, 64.8, 64.3, 59.5, 55.4, 50.8, 39.1, 37.0, 34.7, 34.6, 33.2, 30.0, 29.6, 25.0, 21.7, 20.9, 18.6, 8.2. FTIR (thin film, cm^{-1}) 2966, 2347, 1585, 1464, 1437, 1344, 1255, 1135, 1089, 949. HRMS calculated for $\text{C}_{26}\text{H}_{36}\text{O}_5$ (M^+): 428.25627. Found: 428.25612.



Epoxy cyclooctanone **111**:

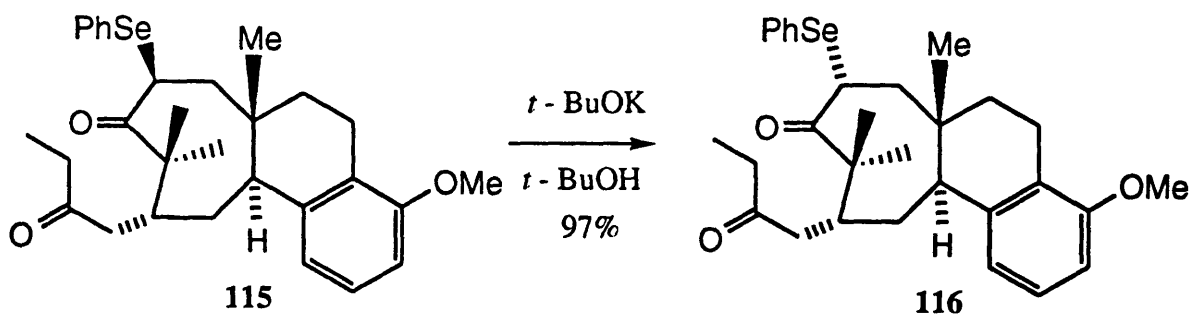
To epoxy cyclooctanol **110** (24 mg, 0.056 mmol) in 3 mL dichloromethane was added pyridinium chlorochromate on neutral alumina (100 g, 1 mmol / g) and 0.1 mL pyridine. The reaction was stirred at room temperature for 18 h, at which time the dark brown suspension was filtered through a silica gel (SiO₂) / anhydrous magnesium sulfate plug, and the solvent was evaporated. The crude product was purified via flash column chromatography (SiO₂, 1:1 ether / hexane) to yield 21 mg (87%) of pure epoxy cyclooctanone **111**. *R_f* 0.15 (1:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.07 (t, 1H, *J* = 8.3 Hz), 6.81 (d, 1H, *J* = 8.3 Hz), 6.61 (d, 1H, *J* = 8.3 Hz), 4.85 - 4.00 (m, 4H, ketal), 3.79 (s, 3H), 3.76 (d, 1H, *J* = 4.9 Hz), 3.17 (d, 1H, *J* = 4.9 Hz), 2.78 (ddd, 1H, *J* = 4.9, 4.9, 17.6 Hz), 2.55 - 2.50 (m, 1H), 2.48 (dd, 1H, *J* = 6.4, 12.2 Hz), 2.38 (dd, 1H, *J* = 2.4, 12.2 Hz), 1.93 (ddd, 1H, *J* = 6.4, 14.2, 15.8 Hz), 1.87 (d, 1H, *J* = 15.1 Hz), 1.80 (ddd, 1H, *J* = 4.9, 13.3, 13.3 Hz), 1.75 - 1.70 (m, 2H), 1.63 (pdq, 2H, *J* = 7.3, 15.8 Hz), 1.35 (dd, 1H, *J* = 8.3, 15.1 Hz), 1.28 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 0.87 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃) δ 210.8, 156.7, 140.5, 126.0, 125.3, 120.1, 111.8, 106.4, 66.7, 64.7, 64.2, 58.8, 55.3, 49.3, 38.1, 37.7, 37.6, 35.4, 34.8, 34.7, 32.7, 30.0, 26.7, 19.2, 18.8, 15.9, 8.3. FTIR (thin film, cm⁻¹) 2936, 2359, 2341, 1711, 1582, 1463, 1254, 1080, 956, 732. HRMS calculated for (M⁺): 428.25627. Found: 428.25612.



Epoxy diketone 113:

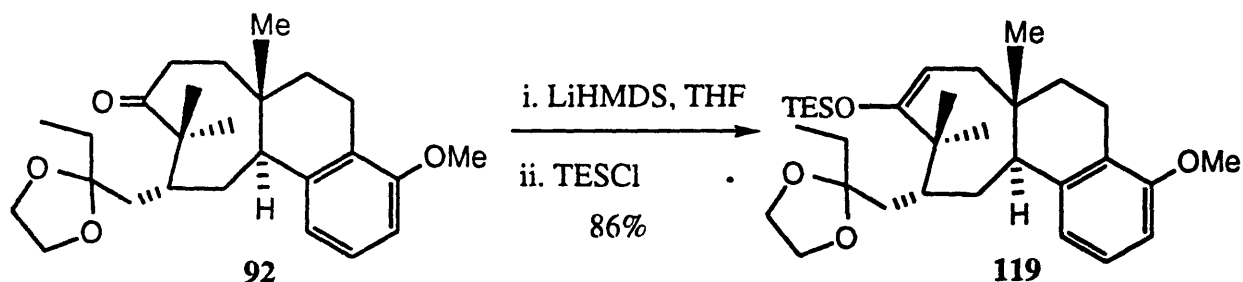
To a solution of epoxy cyclooctanone **111** (19 mg, 0.044 mmol) in 3 mL acetone was added 10% hydrochloric acid (12 μ L). The reaction solution was stirred at room temperature for 18 h, at which time the quenching was performed by the addition of saturated aqueous sodium bicarbonate solution. Following the removal of the acetone *in vacuo*, the product was extracted from the aqueous layer with ether, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 15 mg (88%) pure epoxy diketone **113**. R_f 0.15 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.05 (t, 1H, J = 8.3 Hz), 6.74 (d, 1H, J = 8.3 Hz), 6.61 (d, 1H, J = 8.3 Hz), 3.78 (s, 3H), 3.76 (d, 1H, J = 4.9 Hz), 3.25 (d, 1H, J = 4.9 Hz), 3.10 (dddd, 1H, J = 2.7, 2.7, 9.7, 12.4 Hz), 2.78 (ddd, 1H, J = 3.8, 3.8, 17.5 Hz), 2.56 (dd, 1H, J = 2.7, 17.5 Hz), 2.53 - 2.49 (m, 1H), 2.47 (dd, 1H, J = 7.3, 17.8 Hz), 2.40 (dd, 1H, J = 3.6, 12.7 Hz), 2.34 (dd, 1H, J = 7.3, 17.8 Hz), 2.26 (dd, 1H, J = 9.7, 17.5 Hz), 1.87 (ddd, 1H, J = 3.5, 12.4, 15.1 Hz), 1.87 - 1.75 (m, 1H), 1.75 (ddd, 1H, J = 3.8, 9.2, 12.2 Hz), 1.75 (dd, 1H, J = 3.8, 9.2 Hz), 1.29 (ddd, 1H, J = 2.7, 12.9, 14.8 Hz), 1.26 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H), 1.02 (t, 1H, J = 7.3 Hz). NOE difference experiments were performed to determine the regiochemistry and stereochemistry of the epoxide. ^{13}C NMR (125 MHz, CDCl_3) δ 210.2, 210.0, 156.8, 140.0, 126.0, 125.5, 119.9, 106.6, 66.8, 58.9, 55.3, 48.3, 44.2, 37.6, 37.1, 36.8, 35.0, 34.9, 32.8, 26.4, 19.2, 18.4, 16.1, 7.7. FTIR (thin film, cm^{-1}) 3393, 2928, 2361,

1708, 1702, 1578, 1458, 1373, 1263, 1075, 1026. HRMS calculated for $\text{C}_{24}\text{H}_{32}\text{O}_5$
(M^+): 384.23006. Found: 384.23037.



α -Phenylselenenyldiketone **116**:

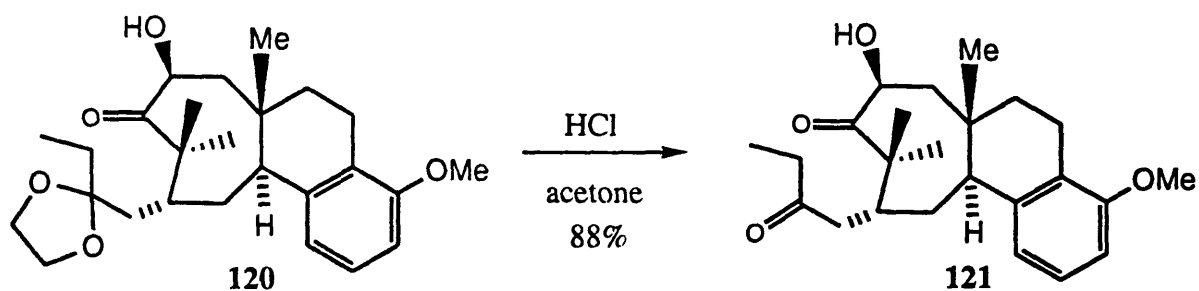
β -phenylselenenyldiketone **115** (6.6 mg, 0.012 mmol) was dissolved in 1.5 mL *tert*-butyl alcohol under argon, and to this solution was added potassium *tert*-butoxide (7 mg, 0.06 mmol). The reaction was stirred at room temperature for 2 h, at which time all starting material had disappeared as evidenced by thin layer chromatography. At this time the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution, and the residue was diluted with ether. The layers were then separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified via flash column chromatography (SiO₂, 20% ether / hexane) to yield 6.4 mg (97%) α -phenylselenenyldiketone **116**. *R_f* 0.55 (1:1 ether / hexane). ¹H NMR (300 MHz, CDCl₃) δ 7.63 - 7.53 (m, 2H), 7.35 - 7.25 (m, 3H), 7.05 (t, 1H, *J* = 8.3 Hz), 6.65 (d, 1H, *J* = 8.3 Hz), 6.58 (d, 1H, *J* = 8.3 Hz), 4.66 (dd, 1H, *J* = 4.8, 14.4 Hz), 3.78 (s, 3H), 3.12 (dddd, 1H, *J* = 2.4, 4.8, 12.0, 17.4 Hz), 2.70 (ddd, 1H, *J* = 5.4, 5.4, 18.6 Hz), 2.59 (dd, 1H, *J* = 3.6, 18.6 Hz), 2.65 - 2.50 (m, 1H), 2.50 - 2.13 (m, 2H), 2.45 (dd, 1H, *J* = 6.6, 18.0 Hz), 2.34 (dd, 1H, *J* = 7.3, 18.6 Hz), 2.23 (d, 1H, *J* = 18.0 Hz), 2.19 (dd, 1H, *J* = 7.3, 18.6 Hz), 2.08 - 1.98 (m, 1H), 2.01 (dd, 1H, *J* = 4.8, 15.6 Hz), 1.60 - 1.30 (m, 2H), 1.18 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.00 (t, 3H, *J* = 7.3 Hz).



Triethylsilyl enol ether **119**:

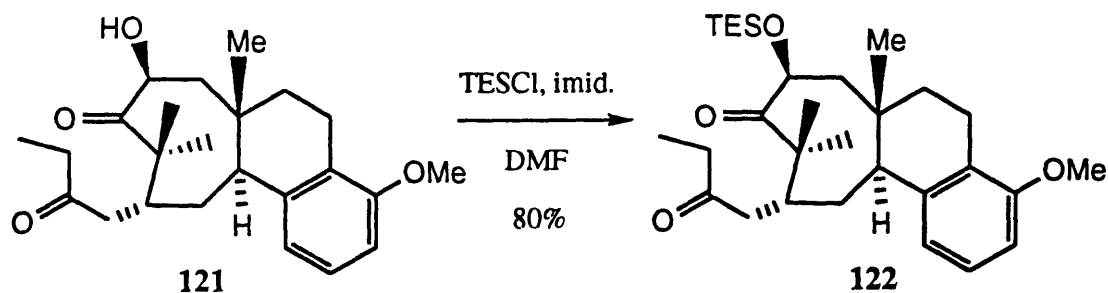
Cyclooctanone **92** (30 mg, 0.07 mmol) was placed in a dry, 25 mL, flask under argon, 3 mL dry tetrahydrofuran was added, and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. Lithium bis(trimethylsilyl)amide (0.13 mL, 0.12 mmol, 0.88 M in tetrahydrofuran) was then added dropwise, the solution was warmed to $0\text{ }^{\circ}\text{C}$, and was stirred at this temperature for 1 h. The reaction was then re-cooled to $-78\text{ }^{\circ}\text{C}$, chlorotriethylsilane (33 mg, 0.22 mmol) was then added, and the reaction was allowed to warm to room temperature. Quenching was performed by the addition of 2 mL saturated aqueous sodium bicarbonate solution, the layers were separated, and the aqueous layer was washed (3 x 2 mL) with ether. The ethereal layers were dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (SiO_2 , 20% ether / hexane) to yield 32.7 mg (86%) triethylsilyl enol ether **119**. R_f 0.88 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.15 - 7.05 (m, 2H), 6.70 - 6.65 (m, 1H), 4.57 (t, 1H, $J = 9.3$ Hz), 4.01 - 3.84 (m, 4H, ketal), 3.81 (s, 3H, OMe), 3.09 (dd, 1H, $J = 3.7, 9.6$ Hz), 2.98 (dd, 1H, $J = 9.3, 14.8$ Hz), 2.80 - 2.68 (m, 1H), 2.72 (dd, 1H, $J = 7.0, 18.7$ Hz), 2.62 (ddd, 1H, $J = 7.0, 13.3, 18.6$ Hz), 2.16 (ddd, 1H, $J = 3.7, 13.3, 16.7$ Hz), 2.0 (d, 1H, $J = 16.0$ Hz), 1.93 (ddd, 1H, $J = 4.7, 4.7, 13.7$ Hz), 1.80 - 1.60 (m, 4H), 1.38 (d, 1H, $J = 6.0$ Hz), 1.33 (dd, 1H, $J = 7.0, 16.0$ Hz), 1.20 (s, 3H), 1.02 - 0.9 (m, 15 H), 0.82 (s, 3H), 0.66 (q, 6H, $J = 8.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3) 160.5, 160.2, 142.8, 125.8, 125.9, 118.4, 112.6, 106.4, 97.9, 64.9, 64.6, 55.3, 44.3, 40.2,

40.1, 39.9, 37.3, 36.6, 36.4, 35.6, 30.5, 28.4, 21.4, 19.7, 19.2, 8.2, 6.9, 5.2. FTIR (thin film, cm^{-1}) 2956, 2876, 1639, 1581, 1475, 1462, 1438, 1377, 1301, 1261, 1188, 1138, 1086, 1065, 1007, 947. HRMS calculated for $\text{C}_{32}\text{H}_{52}\text{O}_4\text{Si}$ ($\text{M}+\text{H}$)⁺: 528.36349. Found: 528.36344.



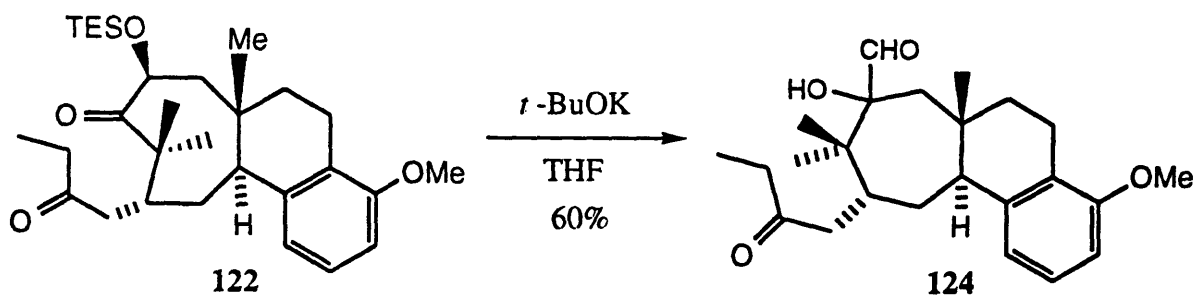
Hydroxy diketone 121:

To a solution of α -hydroxydiketone **120** (19 mg, 0.044 mmol) in 3 mL acetone was added 10% hydrochloric acid (12 μ L). The reaction was stirred at room temperature for 18 h, at which time the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution. Following the removal of the acetone *in vacuo*, the product was extracted from the aqueous layer with ether, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 15 mg (88%) pure hydroxy diketone **120**. R_f 0.20 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.06 (t, 1H, $J = 8.3$ Hz), 6.79 (d, 1H, $J = 8.3$ Hz), 6.63 (d, 1H, $J = 8.3$ Hz), 4.49 (ddd, 1H, $J = 3.4, 3.4, 9.8$ Hz), 3.78 (s, 3H, OMe), 3.70 (dddd, 1H, $J = 3.4, 3.4, 9.8, 15.6$ Hz), 2.71 (ddd, 1H, $J = 2.0, 5.9, 18.1$ Hz), 2.63 (dd, 1H, $J = 2.0, 17.1$ Hz), 2.57 (dd, 1H, $J = 10.7, 15.1$ Hz), 2.57 - 2.48 (m, 1H), 2.50 (dd, 1H, $J = 7.3, 17.6$ Hz), 2.38 (dd, 1H, $J = 7.3, 17.6$ Hz), 2.27 (dd, 1H, $J = 9.8, 17.1$ Hz), 1.98 (dd, 1H, $J = 4.9, 14.7$ Hz), 1.92 (ddd, 1H, $J = 3.4, 11.7, 15.1$ Hz), 1.72 (ddd, 1H, $J = 5.9, 12.7, 12.7$ Hz), 1.61 - 1.54 (m, 2H), 1.52 (ddd, 1H, $J = 2.5, 5.9, 12.7$ Hz), 1.43 (s, 1H), 1.31 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.04 (t, 3H, $J = 7.3$ Hz). FTIR (thin film, cm^{-1}) 3501, 2935, 1711, 1583, 1459, 1438, 1256, 1077, 779, 733.



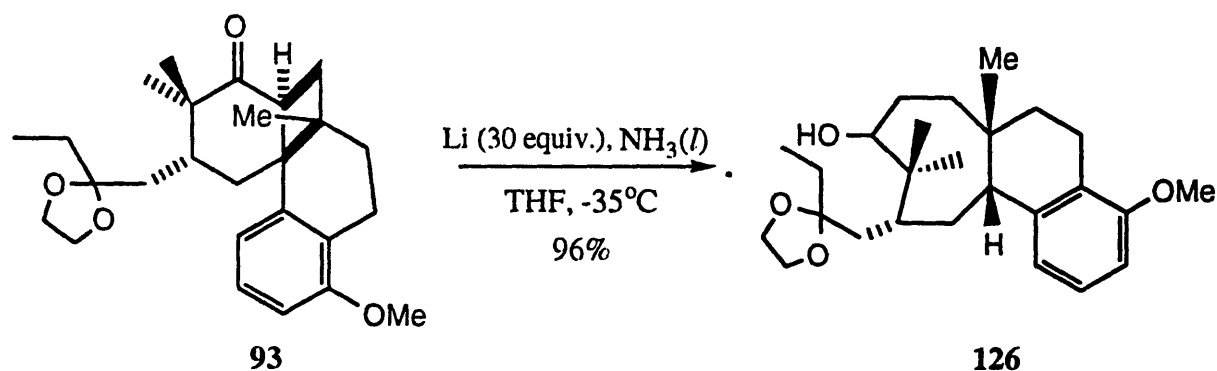
Triethylsiloxy diketone 122:

To a solution of hydroxydiketone **121** (35 mg, 0.09 mmol) in 1.5 mL *N-N*-dimethylformamide under argon was added imidazole (12 mg, 0.18 mmol), and chlorotriethylsilane (30 μ L, 0.18 mmol) at 0 $^{\circ}$ C. The reaction was stirred at 0 $^{\circ}$ C for 20 minutes at which time saturated aqueous sodium bicarbonate solution was added. The resulting solution was diluted with 50 mL water, and was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 36.4 mg (80%) pure triethylsiloxy diketone **122**. R_f 0.85 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.06 (dd, 1H, J = 7.8, 8.3 Hz), 6.79 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 8.3 Hz), 4.48 (dd, 1H, J = 5.4, 8.7 Hz), 3.78 (s, 3H), 2.70 (ddd, 1H, J = 2.4, 4.9, 17.6 Hz), 2.63 (dd, 1H, J = 2.0, 16.6 Hz), 2.59 - 2.37 (m, 3H), 2.49 (dd, 1H, J = 7.3, 17.6 Hz), 2.37 (dd, 1H, J = 7.3, 17.6 Hz), 2.23 (dd, 1H, J = 9.8, 16.6 Hz), 1.87 (dd, 1H, J = 5.4, 15.1 Hz), 1.83 (ddd, 1H, J = 2.9, 12.7, 14.7 Hz), 1.70 - 1.59 (m, 1H), 1.64 (dd, 1H, J = 5.9, 12.2 Hz), 1.49 (ddd, 1H, J = 2.9, 5.4, 12.7 Hz), 1.28 (s, 3H), 1.25 (s, 3H), 1.07 (s, 3H), 1.04 (t, 3H, J = 7.3 Hz), 0.97 (t, 9H, J = 7.8 Hz), 0.64 (q, 6H, J = 7.8 Hz). FTIR (thin film, cm^{-1}) 2924, 1738, 1717, 1694, 1584, 1557, 1463, 1418, 1385, 1246, 1075, 1005.



Cycloheptanal **124**:

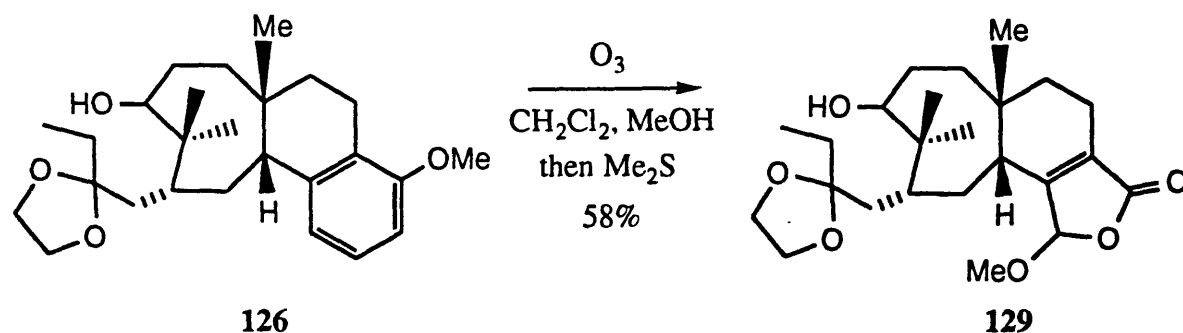
Triethylsiloxy diketone **122** (30 mg, 0.06 mmol) was dissolved in 1 mL tetrahydrofuran under argon, and to this solution was added potassium *tert*-butoxide (50 mg, 0.43 mmol). The reaction was stirred at room temperature for 4 h, during which time the reaction proceeded through one, slightly more polar compound (assumed to be the C(10) epimer), which progressed to another more polar product as evidenced by thin layer chromatography. When both the starting material and the intermediate had reacted, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution, and the residue was diluted with ether. The layers were then separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified via flash column chromatography (SiO_2 , 25% ether / hexane) to yield 14 mg (60%) cycloheptanal **124**. R_f 0.67 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 10.76 (s, 1H), 7.10 (dd, 1H, $J = 7.8, 8.3$ Hz), 6.72 (d, 1H, $J = 8.3$ Hz), 6.62 (1H, $J = 7.8$ Hz), 3.80 (s, 3H), 3.02 (dd, 1H, $J = 2.9, 13.2$ Hz), 3.03 (d, 1H, $J = 12.2$ Hz), 2.85 (ddd, 1H, $J = 2.4, 6.8, 14.7$ Hz), 2.77 (ddd, 1H, $J = 2.9, 2.9, 18.1$ Hz), 2.64 (dd, 1H, $J = 2.4, 17.6$ Hz), 2.45 (dd, 1H, $J = 6.8, 11.2$ Hz), 2.41 (dq, 1H, $J = 7.3, 17.6$ Hz), 2.32 (d, 1H, $J = 12.2$ Hz), 2.32 (dq, 1H, $J = 7.3, 17.6$ Hz), 2.19 (dd, 1H, $J = 9.8, 17.1$ Hz), 1.70 - 1.55 (m, 4H), 1.52-1.46 (m, 1H), 1.31 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 0.99 (t, 3H, $J = 7.3$ Hz).



cis- Cyclooctanol 126:

A 250 mL, 3-necked flask equipped with a stir bar, a rubber septum, a ground glass stopper, and a dry ice condenser fitted with an argon inlet, was cooled to -78°C and was charged with liquid ammonia (120 mL). Lithium metal (282 mg, 30 equiv.), flattened and cut into small pieces, was added to the flask over a period of 15 minutes. The cooling bath was then removed, and the reaction mixture was stirred at -35°C to -33°C for 20 minutes. Cyclobutane **93** (565 mg, 13.6 mmol) in 8 mL dry tetrahydrofuran was added dropwise, via cannula over a period of 10 minutes, and the reaction was stirred at reflux (-33°C) for 30 minutes. At this time, *sec*-butyl alcohol was added slowly, and, at the cessation of the exothermic reaction (~ 15 minutes), the dry ice condenser was removed and the liquid ammonia was allowed to evaporate for 2 h at ambient temperature before water (75 mL) was added. The tetrahydrofuran was then evaporated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and the solvent was then evaporated to afford a pale yellow oil. The crude product was purified via flash column chromatography (SiO_2 , 20% ether / hexanes) to yield 542 mg (96%) of a clear oil. R_f 0.25 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.10 (t, 1H, $J = 7.8$ Hz), 7.04 (d, 1H, $J = 7.8$ Hz), 6.61 (d, 1H, $J = 7.8$ Hz), 4.13 - 3.98 (m, 4H, ketal), 3.98 - 3.81 (m, 1H, carbinol H), 3.81 (s, 3H, OMe), 2.86 (dd, 1H, $J = 6.4, 18.1$ Hz), 2.50 (d, 1H, $J = 13.7$ Hz), 2.45 (ddd, 1H, $J = 7.3, 12.2,$

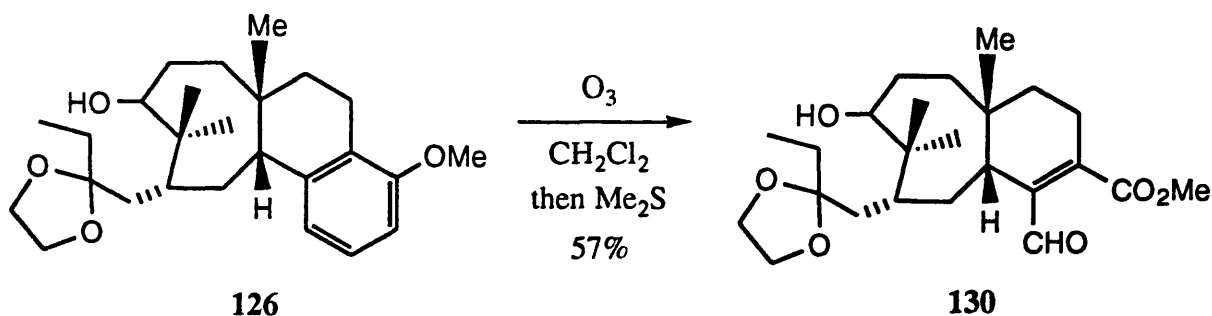
18.1 Hz), 2.09 (ddd, 1H, $J = 5.9, 14.4, 14.4$ Hz), 2.02 (d, 1H, $J = 9.3$ Hz), 1.99 - 1.88(m, 3H), 1.88 - 1.82 (m, 1H), 1.84 (d, 1H, $J = 14.7$ Hz), 1.82 - 1.70 (m, 1H), 1.74 (dd, 1H, $J = 7.8, 10.8$ Hz), 1.69 - 1.52 (m, 4H), 1.48 (dd, 1H, $J = 9.8, 14.2$ Hz), 0.98 (t, 3H, $J = 7.8$ Hz), 0.90 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.7, 148.9, 125.8, 123.9, 122.6, 112.9, 106.1, 74.9, 64.9, 64.5, 55.2, 49.2, 41.2, 40.7, 39.9, 39.2, 38.2, 34.9, 31.7, 30.3, 30.1, 26.3, 20.2, 19.8, 18.9, 8.4. FTIR (thin film, cm^{-1}) 3419, 2961, 2932, 2878, 1584, 1464, 1438, 1255, 1071. HRMS calculated for $\text{C}_{26}\text{H}_{40}\text{O}_4$ (M^+): 416.29266. Found: 416.29313.



Acetal lactone **129**:

To a solution of *cis*-cyclooctanol **126** (48 mg, 0.12 mmol) in 9 mL dichloromethane and 3 mL methanol was added one crystal of Sudan Red III. The resulting pink solution was cooled to $-78\text{ }^{\circ}\text{C}$, and was subjected to ozone until the color faded to clear. Dimethyl sulfide (2 mL) was immediately added, and the reaction was allowed to warm to room temperature, where it was stirred for 4 h. At this time saturated aqueous sodium bicarbonate solution was added and the product was extracted with ether. The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash column chromatography (SiO_2 , 20% ether / hexane) to yield 28 mg (58%) of acetal lactone **129**. R_f 0.19 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 5.73 (t, 1H, $J = 1.5$ Hz), 4.10 - 3.89 (m, 4H, ketal), 3.80 - 3.75 (m, 1H, carbinol H), 3.55 (s, 3H, OMe), 3.36 (d, 1H, $J = 5.9$, OH), 2.33 (dd, 1H, $J = 6.4, 18.6$ Hz), 2.26 (dd, 1H, $J = 3.2, 7.3$ Hz), 2.11 (ddd, 1H, $J = 3.2, 11.2, 17.6$ Hz), 2.05 - 1.93 (m, 2H), 1.86 (ddd, 1H, $J = 6.3, 13.2, 19.0$ Hz), 1.80 (d, 1H, $J = 14.7$ Hz), 1.72 (dd, 1H, $J = 6.3, 13.2$ Hz), 1.69 - 1.59 (m, 6H), 1.47 - 1.40 (m, 2H), 0.91 (t, 3H, $J = 7.8$ Hz), 0.91 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H). DEPT and APT experiments were performed to determine carbon multiplicities. ^{13}C NMR (125 MHz, CDCl_3) δ 171.8 (carbonyl), 163.4 (quaternary), 127.0 (quaternary), 112.4 (quaternary), 102.4 (CH), 75.1 (CH), 64.9 (CH_2), 64.1 (CH_2), 56.7 (CH_3), 42.8 (CH), 40.6

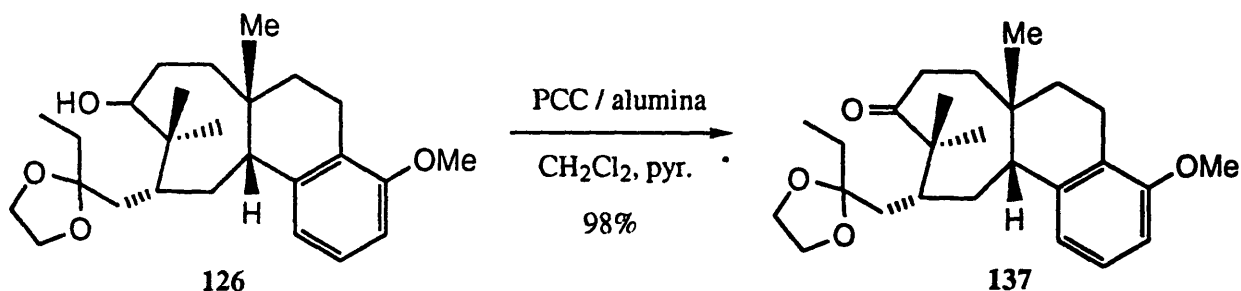
(quaternary), 40.3 (CH₂), 38.4 (CH), 37.3 (CH₂), 35.7 (quaternary), 33.6 (CH₂), 31.1 (CH₂), 30.1 (CH₂), 28.8 (CH₃), 27.2 (CH₂), 20.2 (CH₃), 19.6 (CH₃), 17.5 (CH₂), 8.4 (CH₃). HETCOR and COSY-90 experiments were also performed to determine structure and coupling partners. FTIR (thin film, cm⁻¹) 3500, 2935, 1765, 1709, 1683, 1463, 1365, 1203, 1130, 1075, 1047. HRMS calculated for C₂₄H₃₈O₆ (M+H)⁺: 422.26684. Found: 423.26672.



Aldehyde Ester 130:

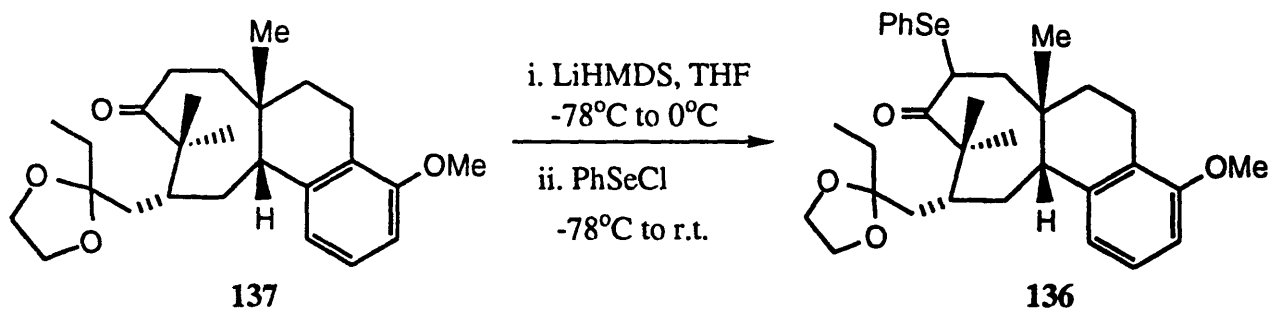
To a solution of *cis*-cyclooctanol **126** (170 mg, 0.41 mmol) in 9 mL dichloromethane was added one crystal of Sudan Red III. The resulting pink solution was cooled to -78 °C, and was subjected to ozone until the color faded to clear. Dimethyl sulfide (2 mL) was immediately added, and the reaction solution was allowed to warm to room temperature, where it was stirred for 4 h. At this time saturated aqueous sodium bicarbonate solution was added, the layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (SiO₂, 20% ether / hexane) to yield 99 mg (57%) of pure aldehyde ester **130**. *R_f* 0.21 (2:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 9.88 (s, 1H, aldehyde H), 4.20 - 3.85 (m, 4H, ketal), 3.85 - 3.81 (m, 1H, carbinol H), 3.79 (s, 3H, OMe), 2.68 (d, 1H, *J* = 8.8 Hz), 2.48 (dd, 1H, *J* = 5.9, 20.0 Hz), 2.33 (dddd, 1H, *J* = 1.5, 6.8, 11.2, 20.0 Hz), 1.94 (ddd, 1H, *J* = 3.0, 6.5, 9.0 Hz), 1.89 - 1.79 (m, 2H), 1.79 (d, 1H, *J* = 14.6 Hz), 1.76 - 1.54 (m, 4H), 1.51 (ddd, 1H, *J* = 6.4, 9.5, 16.1 Hz), 1.44 - 1.36 (m, 3H), 1.33 (dd, 1H, *J* = 8.8, 14.6 Hz), 0.94 (s, 3H), 0.90 (t, 3H, *J* = 7.5 Hz), 0.86 (s, 3H), 0.81 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 194.0, 168.5, 146.7, 136.6, 111.8, 75.6, 64.5, 63.9, 51.7, 42.5, 40.5, 40.5, 40.4, 38.1, 37.1, 34.7, 33.6, 30.38, 29.7, 27.1, 26.6, 24.0, 18.9, 7.8. FTIR (thin film, cm⁻¹) 3503, 2967, 2934, 2879, 1798,

1703, 1626, 1464, 1435, 1363, 1261, 1201, 1098, 1058, 922, 732. HRMS calculated for $\text{C}_{24}\text{H}_{38}\text{O}_6$ (M^+): 422.26684. Found: 422.26662.



cis -Cyclooctanone 137:

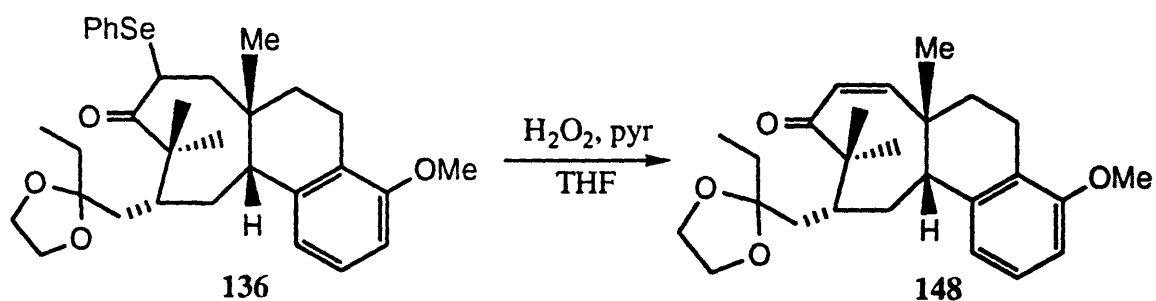
To *cis* -cyclooctanol **126** (540 mg, 1.30 mmol) in 10 mL dichloromethane was added pyridinium chlorochromate on neutral alumina (1.7 g, 1 mmol / g), and 0.2 mL pyridine. The reaction was stirred at room temperature for 16 h, at which time the dark brown suspension was filtered through a silica gel / anhydrous magnesium sulfate plug, and the solvent was evaporated. The crude product was purified via flash column chromatography (SiO₂, 20% ether / hexane) to yield 528 mg (98%) of pure *cis* -cyclooctanone **137**. *R_f* 0.52 (1:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.04 (t, 1H, *J* = 7.8 Hz), 6.73 (d, 1H, *J* = 7.8 Hz), 6.58 (d, 1H, *J* = 7.8 Hz), 4.00 - 3.80 (m, 4H, ketal), 3.79 (s, 3H, OMe), 2.72 (dd, 1H, *J* = 6.4, 18.1 Hz), 2.67 (d, 1H, *J* = 5.4 Hz), 2.66 (d, 1H, *J* = 5.4 Hz), 2.44 (ddd, 1H, *J* = 7.3, 12.7, 18.1 Hz), 2.44 - 2.41 (m, 1H), 2.26 (ddd, 1H, *J* = 8.8, 8.8, 15.6 Hz), 2.10 (ddd, 1H, *J* = 4.9, 8.8, 8.8 Hz), 1.73 (d, 1H, *J* = 13.7 Hz), 1.72 - 1.68 (m, 1H), 1.67 - 1.58 (m, 4H), 1.35 - 1.24 (m, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 0.88 (s, 3H), 0.86 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃) δ 220.8, 156.7, 144.6, 125.8, 122.5, 122.2, 112.1, 106.2, 64.9, 64.3, 55.0, 50.7, 46.2, 45.4, 39.6, 39.5, 37.8, 36.3, 35.0, 30.7, 30.4, 27.1, 22.5, 20.1, 17.9, 8.2. FTIR (thin film, cm⁻¹) 2967, 2931, 1684, 1586, 1465, 1437, 1255, 1198, 1081, 1059. HRMS calculated for C₂₆H₃₈O₄ (M⁺): 414.277104. Found: 414.27716.



***cis*- α - Phenylselenenylketone 136:**

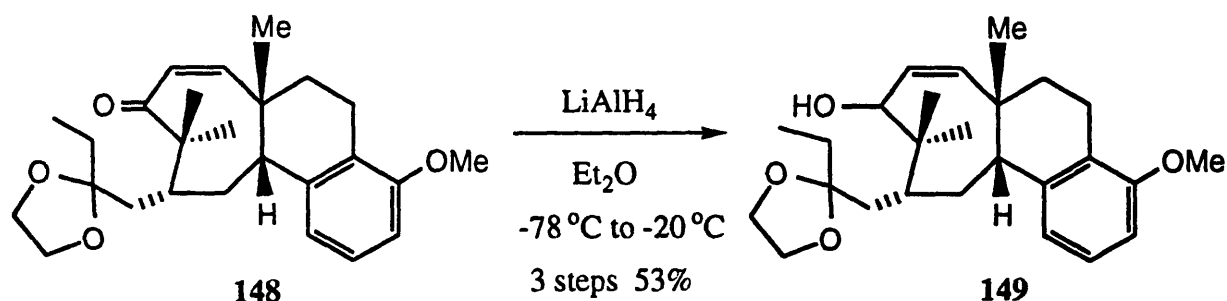
A solution of *cis* - cyclooctanone **137** (59 mg, 0.14 mmol) in 2 mL tetrahydrofuran under argon, was cooled to -78°C , and to it was added dropwise lithium bis(trimethylsilyl)amide (0.32 mL, 0.28 mmol, 0.88 M in tetrahydrofuran). The solution was warmed to 0°C , and was stirred at this temperature for 2 h. The reaction mixture was then recooled to -78°C , and phenylselenium chloride (54 mg, 0.28 mmol) in 0.5 mL tetrahydrofuran was added via cannula. The reaction mixture was then warmed to room temperature, and was stirred for 15 minutes before the reaction was quenched by the addition of 2 mL saturated aqueous sodium bicarbonate solution. The tetrahydrofuran was then evaporated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give a yellow oil that was carried directly onto the next reaction. The *cis* - α -phenylselenenylketone **136** was partially purified via preparative thin layer chromatography (SiO_2 , 3% ether / hexane) to yield 3 mg of pure *cis* - α -phenylselenenylketone **136** for characterization. R_f 0.52 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) 7.60-7.56 (m, 2H, PhSe), 7.35 - 7.30 (m, 3H, PhSe), 7.01 (t, 1H, $J = 7.8$ Hz), 6.72 (d, 1H, $J = 7.8$ Hz), 6.58 (d, 1H, $J = 7.8$ Hz), 4.36 (dd, 1H, $J = 3.9, 11.2$ Hz), 3.95 - 3.78 (m, 4H ketal), 3.77 (s, 3H, OMe), 2.63 (dd, 1H, $J = 7.3, 18.6$ Hz), 2.55 (dd, 1H, $J = 11.2, 15.1$ Hz), 2.59 - 2.50 (m, 1H), 2.36 (d, 1H, $J = 6.3$ Hz), 2.17 (dd, 1H, $J = 3.4, 15.1$ Hz), 2.06 (t, 1H, $J = 7.8$ Hz), 1.90 - 1.78 (m, 3H), 1.71 (d, 1H, $J = 14.2$ Hz), 1.61 - 1.55 (m, 2H), 1.25 - 1.19 (m, 2H),

1.27 (s, 3H), 1.14 (s, 3H), 0.85 (t, 3H, $J = 7.8$ Hz), 0.80 (s, 3H). FTIR (thin film, cm^{-1}) 2930, 1681, 1586, 1467, 1438, 1256, 1077, 740. HRMS calculated for $\text{C}_{32}\text{H}_{42}\text{O}_4\text{Se}$ (M^+): 570.22483. Found: 570.22451.



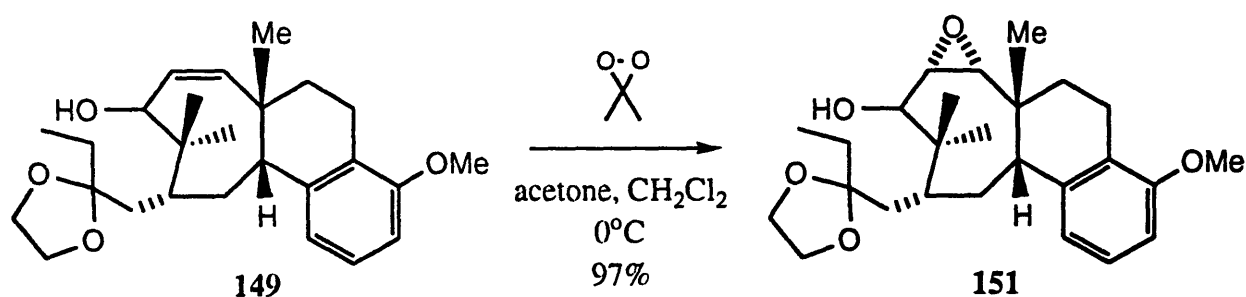
***cis* - Enone 148:**

To a solution of crude *cis* - α -phenylselenylketone **136** in 3 mL tetrahydrofuran was added 0.1 mL pyridine and 0.2 mL hydrogen peroxide (30% in H₂O). The reaction was stirred at room temperature for 24 h, at which time saturated aqueous sodium bicarbonate solution was added. After the removal of the tetrahydrofuran *in vacuo*, the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield an inseparable mixture of enone **148** and starting ketone **137** that was carried directly, without further purification, to the next step. HRMS calculated for C₂₆H₃₆O₄ (M⁺): 412.26359. Found: 412.26321.



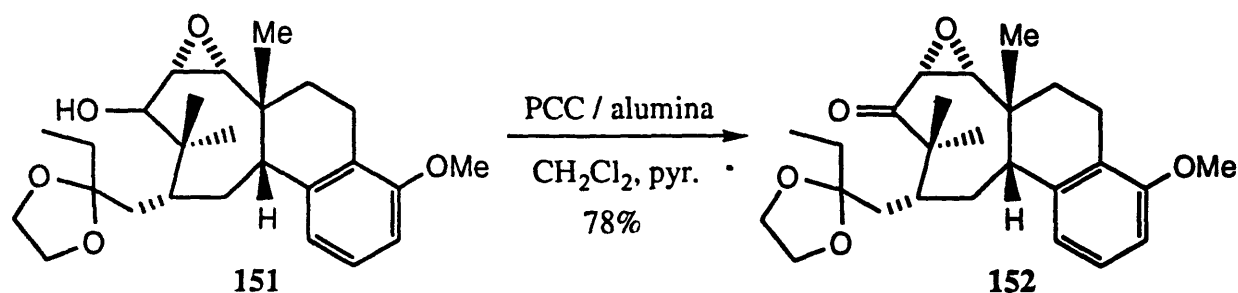
Allylic alcohol 149:

To a -78 °C solution of the enone **148** / ketone **137** mixture in 3 mL dry tetrahydrofuran under argon was added dropwise lithium aluminum hydride (0.23 mL, 0.17 mmol, 0.75 M in hexanes). The reaction was stirred at -78 °C for 10 minutes, and the reaction was then allowed to slowly warm to -20 °C. The reaction was then quenched by the addition of ethyl acetate followed by a saturated aqueous solution of sodium bicarbonate. After the layers were separated, the aqueous layer was washed with ether. The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (SiO₂, 20% ether / hexane) to yield 31 mg (53% for 3 steps) of pure allylic alcohol **149** as a single diastereomer. *R_f* 0.39 (1:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.11 (t, 1H, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 8.0 Hz), 6.62 (d, 1H, *J* = 8.0 Hz), 5.65 (d, 1H, *J* = 12.5 Hz), 5.34 (dd, 1H, *J* = 8.3, 12.5 Hz), 4.54 (d, 1H, *J* = 8.3 Hz), 4.10 - 3.92 (m, 4H, ketal), 3.80 (s, 3H, OMe), 2.81 (dd, 1H, *J* = 6.0, 17.5 Hz), 2.69 (d, 1H, *J* = 11.5 Hz), 2.50 (ddd, 1H, *J* = 7.5, 12.0, 17.5 Hz), 1.92 (ddd, 1H, *J* = 5.5, 12.0, 16.0 Hz), 1.78 (d, 1H, *J* = 14.0 Hz), 1.80 - 1.65 (m, 3H), 1.6 - 1.45 (m, 1H), 1.42 - 1.30 (m, 2H), 1.03 (s, 3H), 0.94 (t, 3H, *J* = 7.8 Hz), 0.82 (s, 3H), 0.80 (s, 3H). FTIR (thin film, cm⁻¹) 3451, 2965, 2875, 1585, 1464, 1257, 1077, 778. HRMS calculated for C₂₆H₃₈O₄ (M⁺): 414.27710. Found: 414.27716.



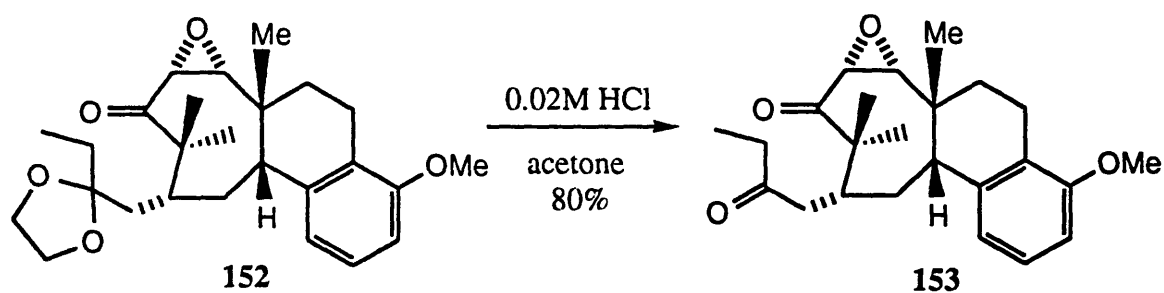
Epoxy alcohol 151:

To a solution of allylic alcohol **149** (5.1 mg, 0.012 mmol) in 1 mL dichloromethane at 0 °C was added a solution of dimethyldioxirane (30 - 40% molar excess) in acetone (0.08 - 0.11 M). The reaction was stirred at 0 °C for 45 minutes at which time the solvents were evaporated to yield 5 mg (97%) of pure epoxy alcohol **151** as a single diastereomer. R_f 0.15 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.11 (t, 1H, $J = 7.8$ Hz), 7.01 (d, 1H, $J = 7.8$ Hz), 6.64 (d, 1H, $J = 7.8$ Hz), 4.14 - 3.98 (m, 4H, ketal), 3.80 (s, 3H, OMe), 3.67 (d, 1H, $J = 9.0$ Hz), 2.98 (d, 1H, $J = 4.9$ Hz), 2.96 (dd, 1H, $J = 4.9, 9.0$ Hz), 2.82 (d, $J = 10.7$ Hz), 2.78 (dd, 1H $J = 7.3, 18.6$ Hz), 2.48 (ddd, 1H, $J = 7.8, 10.7, 18.6$ Hz), 1.94 (d, 1H, $J = 3.0$ Hz), 1.87 (d, 1H, $J = 14.7$ Hz), 1.81 - 1.60 (m, 6H), 1.52 (ddd, 1H, $J = 1.5, 13.0, 14.7$ Hz), 1.15 (s, 3H), 1.04 (s, 3H), 0.97 (t, 3H, $J = 7.3$ Hz), 0.81 (s, 3H). FTIR (thin film, cm^{-1}) 3401, 2930, 2874, 1586, 1468, 1441, 1383, 1257, 1076, 778.



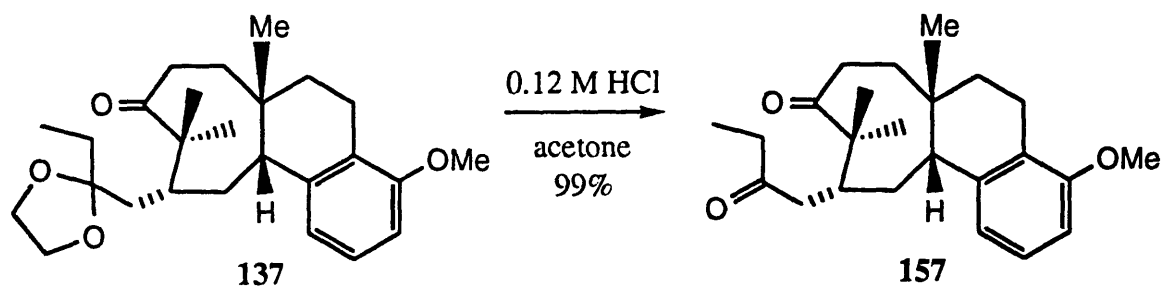
Epoxy cyclooctanone 152:

To epoxy alcohol **151** (3 mg, 0.007 mmol) in 1 mL dichloromethane was added pyridinium chlorochromate on neutral alumina (10 mg, 1 mmol / g), and pyridine (50 μ L). The reaction was stirred at room temperature for 48 h, at which time the dark brown suspension was filtered through a silica gel (SiO_2) / anhydrous magnesium sulfate plug, and the solvent was evaporated. The crude product was purified via flash column chromatography (SiO_2 , 1:1 ether / hexane) to yield 2.3 mg (78%) of pure epoxy cyclooctanone **152**. R_f 0.19 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 1.77 (dd, 1H, $J = 7.8$ Hz), 6.90 (d, 1H, $J = 7.8$ Hz), 6.62 (d, 1H, $J = 7.8$ Hz), 4.17 - 3.90 (m, 4H), 3.83 (d, 1H, $J = 5.9$ Hz), 3.77 (s, 3H, OMe), 3.19 (d, 1H, $J = 5.9$ Hz), 2.87 (d, 1H, $J = 10.8$ Hz), 2.65 (dd, 1H, $J = 7.8, 19.0$ Hz), 2.42 (ddd, 1H, $J = 9.8, 11.2, 19.0$ Hz), 2.30 - 2.20 (m, 2H), 1.84 (d, 1H, $J = 14.7$ Hz), 1.76 (pq, 2H $J = 7.3$ Hz), 1.63 - 1.58 (m, 1H), 1.43 - 1.38 (m, 2H), 1.28 (s, 3H), 1.12 (s, 3H), 0.98 (t, 3H, $J = 7.3$ Hz), 0.92 (s, 3H).



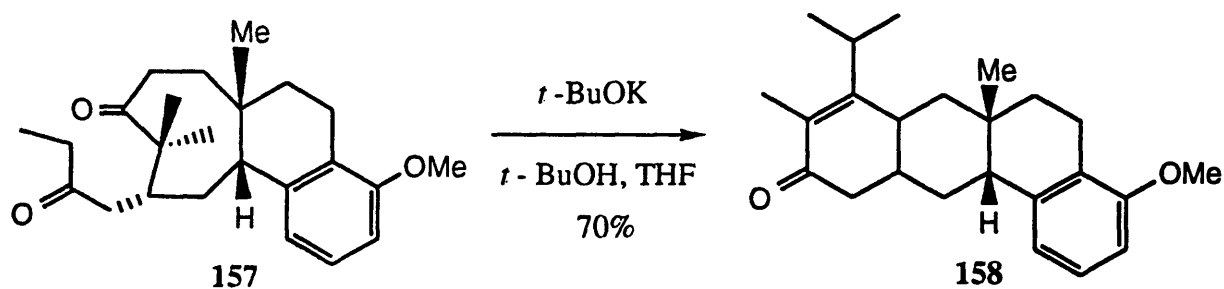
Epoxy diketone 153:

To a solution of Epoxy cyclooctanone **152** (2.3 mg; 0.005 mmol) in 3 mL acetone was added 10% hydrochloric acid (6 μ L). The reaction was stirred at room temperature for 18 h, at which time the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution. Following the removal of the acetone *in vacuo*, the product was extracted from the aqueous layer with ether, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield 1.5 mg (80%) pure epoxy diketone **153**. R_f 0.19 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.05 (dd, 1H, $J = 7.3, 8.3$ Hz), 3.83 (d, 1H, $J = 5.4$ Hz), 3.77 (s, 1H, OMe), 3.23 (d, 1H, $J = 5.4$ Hz), 3.16 (d, 1H, $J = 10.7$ Hz), 2.82 (dd, 1H, $J = 2.1, 11.7$ Hz), 2.64 (dd, 1H, $J = 7.8, 19.1$ Hz), 2.57 (dd, 1H, $J = 4.4, 17.6$ Hz), 2.61 - 2.51 (m, 1H), 2.46 (d, 1H, $J = 7.3$ Hz), 2.43 (d, 1H, $J = 8.3$ Hz), 2.50 - 2.40 (m, 1H), 2.36 (d, 1H, $J = 10.7$ Hz), 2.33 (d, 1H, $J = 11.7$ Hz), 2.07 - 2.00 (m, 1H), 1.45 - 1.35 (m, 1H), 1.28 (s, 3H), 1.21 (t, 3H, $J = 7.3$ Hz), 1.14 (s, 3H), 0.95 (s, 3H). FTIR (thin film, cm^{-1}) 3293, 2924, 2851, 2362, 2341, 1718, 1648, 1587, 1465, 1375, 1261, 1079. HRMS calculated for $\text{C}_{24}\text{H}_{32}\text{O}_4$ (M^+): 384.23006. Found: 384.23035.



***cis* -Diketone 157:**

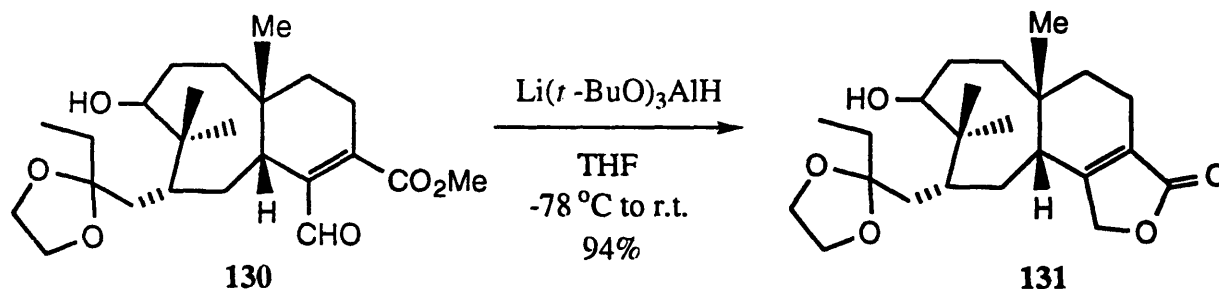
To a solution of *cis* -cyclooctanone **137** (17 mL, 0.04 mmol) in 2 mL acetone was added 10% hydrochloric acid (6 μ L). The reaction was stirred at room temperature for 16 h, at which time a saturated aqueous sodium bicarbonate solution was added, and the acetone was evaporated. The aqueous layer was then extracted with ether, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to yield 14.7 mg pure *cis* -diketone **157** (99%). R_f 0.52 (1:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 7.10 (dd, 1H, $J = 7.8, 8.3$ Hz), 6.75 (d, 1H, $J = 7.8$ Hz), 6.58 (d, 1H, $J = 8.3$ Hz), 3.78 (s, 3H, OMe), 2.71 (dd, 1H, $J = 6.4, 18.1$ Hz), 2.69 (d, 1H, $J = 5.4$ Hz), 2.67 (d, 1H, $J = 5.4$ Hz), 2.59 (dddd, 1H, $J = 2.0, 2.0, 10.3, 13.2$ Hz), 2.51 - 2.45 (m, 1H), 2.46 (d, 1H, $J = 17.6$ Hz), 2.44 (ddd, 1H, $J = 6.8, 12.2, 18.6$ Hz), 2.30 (pq, $J = 7.3$ Hz), 2.23 (ddd, 1H, $J = 2.0, 7.8, 14.7$ Hz), 2.15 (dd, 1H, $J = 10.7, 16.1$ Hz), 1.73 (ddd, 1H, $J = 5.9, 10.7, 16.6$ Hz), 1.61 (dd, 1H, $J = 4.9, 10.3$ Hz), 1.60 - 1.57 (m, 1H), 1.55 (dd, 1H, $J = 6.8, 13.2$ Hz), 1.24 (s, 3H), 1.16 (s, 3H), 1.00 (t, 3H, $J = 7.3$ Hz), 0.89 (s, 3H). FTIR (thin film, cm^{-1}) 2926, 2350, 2251, 1714, 1682, 1586, 1468, 1434, 1367, 1256, 1195, 1078, 986, 912.



***cis* -Tetracycle 158:**

To *cis* -Diketone **157** (20 mg, 0.054 mmol) was added 0.25 mL dry tetrahydrofuran and 0.25 mL *tert*- butyl alcohol under argon. In one portion, potassium *tert*-butoxide (61 mg, 0.54 mmol) was added, and the reaction was stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate was then added, and the tetrahydrofuran was removed *in vacuo*. The product was extracted from the aqueous layer with ether, and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to afford a yellow oil which was purified via flash column chromatography (SiO₂, 20% ether / hexane) to yield 14 mg (70%) of a single diastereomer of tetracycle **158**. *R_f* 0.56 (1:1 ether / hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.11 (t, 1H *J* = 7.8 Hz), 6.70 (d, 1H, *J* = 7.8 Hz), 6.67 (d, 1H, *J* = 7.8 Hz), 3.82 (s, 3H, OMe), 2.94 (sept., 1H, *J* = 7.3 Hz), 2.58 (ddd, 1H, *J* = 6.8, 11.7, 18.6 Hz), 2.43 (dd, 1H, *J* = 5.4, 12.7 Hz), 2.45 - 2.37 (m, 1H), 2.34 (dd, 1H, *J* = 2.9, 15.1 Hz), 2.27 - 2.20 (m, 1H), 2.19 (dd, 1H, *J* = 2.5, 13.2 Hz), 2.15 (ddd, 1H, *J* = 7.3, 13.2, 13.2 Hz), 2.06 (t, 1H, *J* = 15.1 Hz), 1.83 (d, 3H, *J* = 2.5 Hz), 1.24 (d, 3H, *J* = 7.3 Hz), 1.23 (d, 1H, *J* = 7.3 Hz), 1.16 (d, 1H, *J* = 7.3 Hz), 1.12 (d, 1H, *J* = 6.8 Hz), 0.96 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 199.6, 164.5, 157.0, 141.7, 132.0, 126.1, 123.2, 121.8, 106.8, 55.2, 46.4, 45.1, 43.8, 40.9, 40.5, 40.3, 32.9, 31.8, 27.2, 26.9, 21.0, 20.2, 19.3, 11.8. FTIR (thin

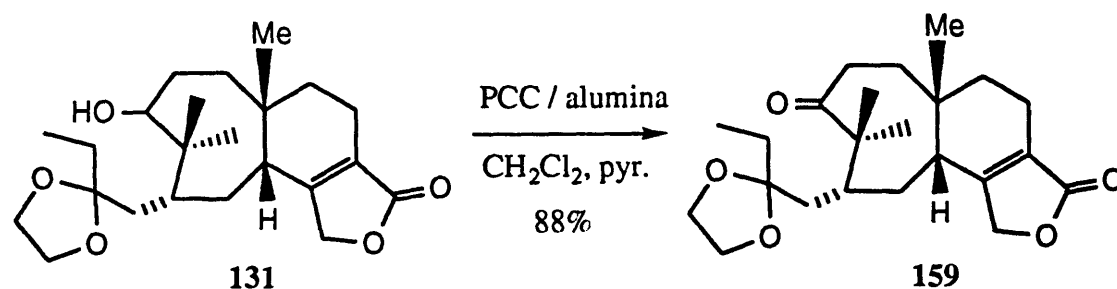
film, cm^{-1}) 2930, 1666, 1585, 1468, 1317, 1258, 1196, 1091, 910, 779, 736. HRMS
calculated for $\text{C}_{24}\text{H}_{32}\text{O}_2$ (M^+): 352.24023. Found: 352.24039.



Lactone 131:

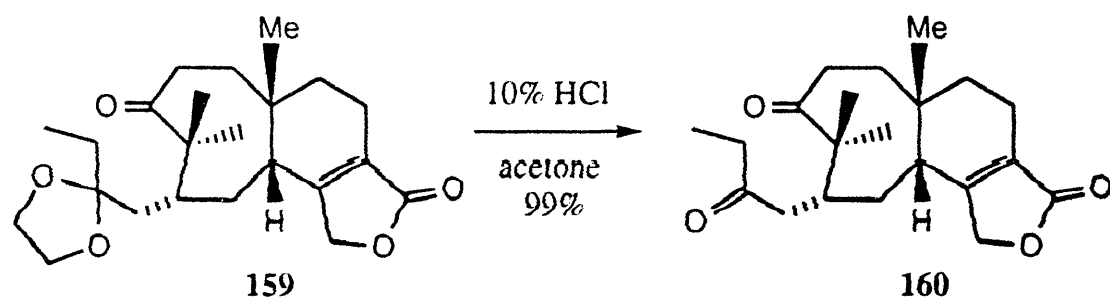
To a solution of ester aldehyde **130** (32.2 mg, 0.076 mmol) in 2 mL dry tetrahydrofuran at $-78\text{ }^{\circ}\text{C}$ was added lithium tri-*tert*-butoxyaluminumhydride (0.8 mL, 0.2 mmol, 0.25 M in tetrahydrofuran made immediately prior to the reaction). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 minutes before it was warmed to $-15\text{ }^{\circ}\text{C}$. Quenching was performed by the addition of a saturated aqueous sodium bicarbonate solution, and the tetrahydrofuran was evaporated. The aqueous layer was then extracted with ether and the combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford a pink oil. The crude product was purified via flash column chromatography (SiO_2 , 2:1 ether / hexane) to yield 28 mg (94%) pure lactone **131**. R_f 0.13 (2:1 ether / hexane). ^1H NMR (500 MHz, CDCl_3) δ 4.88 (ddd, 1H, $J = 2.4, 2.4, 16.6$ Hz), 4.55 (dd, 1H, $J = 3.4, 16.6$ Hz), 4.20 - 3.90 (m, 4H, ketal), 3.80 (dd, 1H, $J = 4.4, 10.3$ Hz), 2.34 (dd, 1H, $J = 5.4, 17.1$ Hz), 2.21 (d, 1H, $J = 10.7$ Hz), 2.18 - 2.08 (br m, 1H), 2.05 - 1.95 (m, 1H), 2.00 (dd, 1H, $J = 4.9, 12.2$ Hz), 1.94 - 1.85 (m, 3 H), 1.83 (d, 1H, 14.2 Hz), 1.77 - 1.57 (m, 6 H), 1.49 (ddd, 1H, $J = 2.9, 2.9, 15.1$ Hz), 1.45 (dd, 1H, $J = 6.3, 13.2$ Hz), 1.42 (s, 1H, OH), 1.37 (dd, 1H, $J = 10.7, 14.2$ Hz), 0.93 (t, 3H, $J = 7.3$ Hz), 0.93 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H). ^{13}H NMR (125 MHz, CDCl_3) δ 174.3, 165.9, 123.4, 112.8, 75.1, 71.2, 64.6, 64.3, 44.3, 40.5, 40.0, 39.0, 37.4, 35.8, 33.7, 30.8, 29.6, 28.8, 27.1, 20.2, 19.5, 17.5, 8.1. FTIR (thin film, cm^{-1}) 3481, 2966, 2932, 2359, 2342, 2249, 1748, 1673, 1464, 1364, 1346, 1259, 1202, 1145, 1099,

1064, 1034, 1011. HRMS calculated for $C_{23}H_{36}O_5$ (M+H)⁺: 392.25628. Found:
392.25610.



Keto lactone 159:

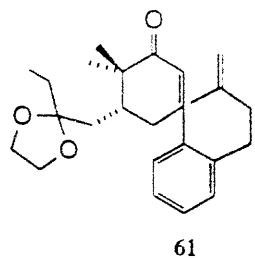
To lactone **131** (24 mg, 0.061 mmol) in 2 mL dichloromethane was added pyridinium chlorochromate on neutral alumina (100 mg, 1 mmol / g), and 0.1 mL pyridine. The reaction was stirred at room temperature for 12 h, at which time the dark brown suspension was filtered through a silica gel (SiO₂) / anhydrous magnesium sulfate plug, and the solvent was evaporated. The crude product was purified via flash column chromatography (SiO₂, 30% ethyl acetate / hexane) to yield 21 mg (88%) of pure keto lactone **159**. *R_f* 0.19 (30% ethyl acetate / hexane). ¹H NMR (500 MHz, CDCl₃) δ 4.96 (ddd, 1H, *J* = 2.4, 2.4, 17.1 Hz), 4.50 (dd, 1H, *J* = 3.4, 17.1 Hz), 3.87 - 3.97 (m, 4H, ketal), 2.71 (ddd, 1H, *J* = 4.9, 4.9, 13.7 Hz), 2.62 (ddd, 1H, *J* = 4.9, 13.2, 13.2 Hz), 2.30 (dd, 1H, *J* = 4.9, 14.7 Hz), 2.24 (dd, 1H, *J* = 4.9, 17.1 Hz), 2.17 - 2.07 (br m, 1H), 1.91 (br s, 1H), 1.73 (d, 1H, *J* = 14.7 Hz), 1.74 - 1.51 (m, 7 H), 1.46 (ddd, 1H, *J* = 5.9, 13.2, 13.2 Hz), 1.30 - 1.91 (m, 2H), 1.24 (s, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.89 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃) δ 220.8, 174.2, 165.5, 122.3, 112.1, 71.0, 64.6, 64.6, 50.3, 45.5, 41.7, 39.0, 37.2, 36.2, 35.1, 34.3, 31.7, 29.8, 27.0, 21.7, 17.7, 17.3, 8.1. FTIR (thin film, cm⁻¹) 2968, 2929, 2363, 1752, 1731, 1701, 1685, 1347, 1251, 1096, 1025, 920, 713. HRMS calculated for C₂₃H₃₄O₅ (M+H)⁺: 390.24062. Found: 390.24107.



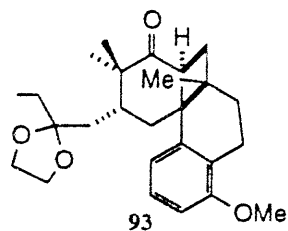
Diketo lactone **160**:

To a solution of keto lactone **159** (19 mg, 0.049 mmol) in 3 mL acetone was added 10% hydrochloric acid (12 μ L). The reaction solution was stirred at room temperature for 18 h, at which time quenching of the reaction was performed by the addition of a saturated aqueous sodium bicarbonate solution. Following the removal of the acetone *in vacuo*, the product was extracted from the aqueous layer with ether, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 17 mg (99%) pure diketone **160** as a white solid. m.p. = 189 - 190 $^{\circ}$ C. R_f 0.19 (30% ethyl acetate / hexane). ^1H NMR (500 MHz, CDCl_3) δ 5.03 (ddd, 1H, J = 2.4, 2.4, 17.1 Hz), 4.61 (dd, 1H, J = 3.4, 17.1 Hz), 2.70 (ddd, 1H, J = 4.9, 4.9, 13.2 Hz), 2.62 (ddd, J = 4.9, 13.2, 13.2 Hz), 2.51 (d, 1H, J = 17.1 Hz), 2.46 (dq, 1H, J = 7.3, 17.6 Hz), 2.34 (dq, 1H, J = 7.3, 17.6 Hz), 2.30 - 2.15 (m, 6H), 1.98 (br s, 1H), 1.54 (ddd, 1H, J = 4.9, 4.9, 14.7 Hz), 1.51 (dd, 1H, J = 4.4, 9.8 Hz), 1.43 - 1.35 (m, 2H), 1.28 (s, 3H), 1.09 (s, 3H), 1.04 (t, 3H, J = 7.3 Hz), 0.92 (s, 3H). HRMS calculated for $\text{C}_{22}\text{H}_{30}\text{O}_4$ (M^+): 346.21441. Found: 346.21425.

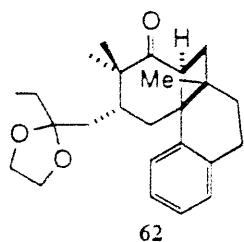
Index of Selected Spectra



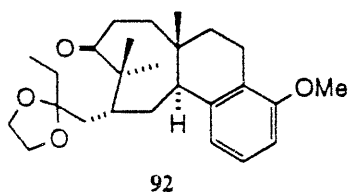
^1H NMR, p. 195



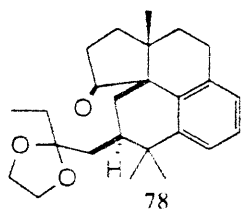
^1H NMR, p. 204



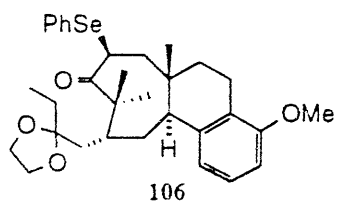
^1H NMR, p. 196
COSY-90, p. 197
nOe, p. 198



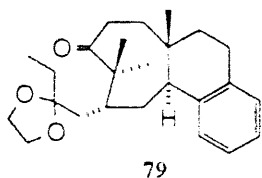
^1H NMR, p. 205
nOe, pp. 206-207
COSY-90, p. 208



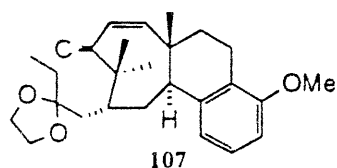
^1H NMR, p. 199



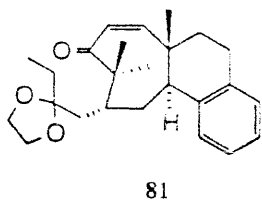
^1H NMR, p. 209



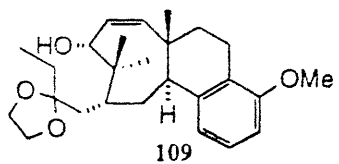
^1H NMR, p. 200



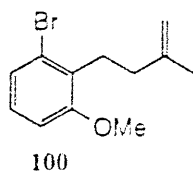
^1H NMR, p. 210
nOe, p. 211



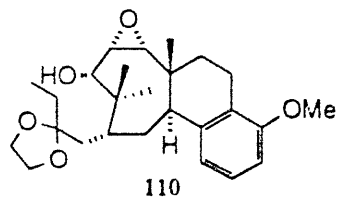
^1H NMR, p. 201



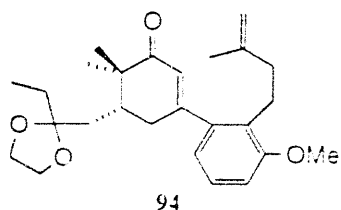
^1H NMR, p. 212



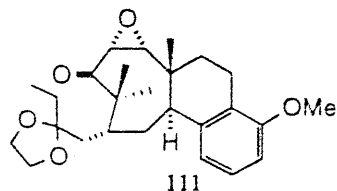
^1H NMR, p. 202



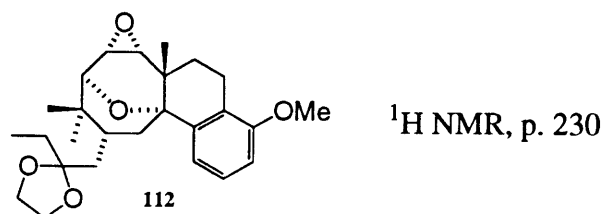
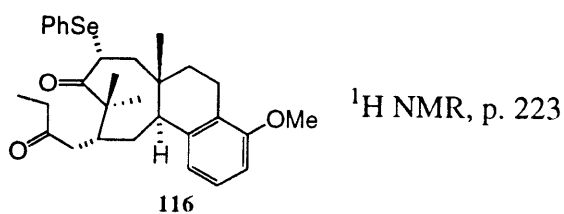
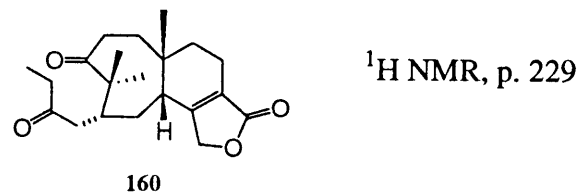
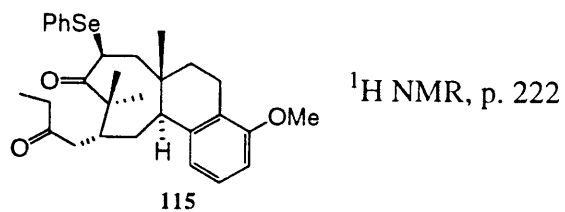
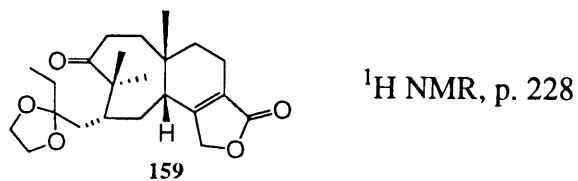
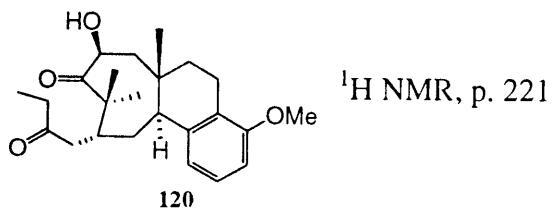
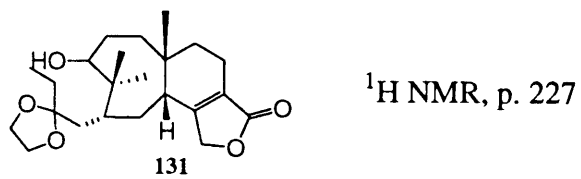
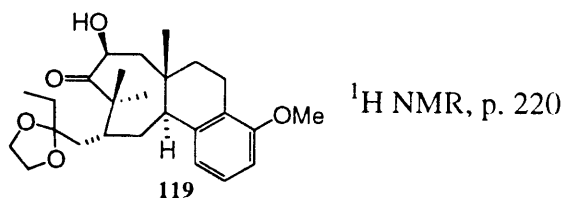
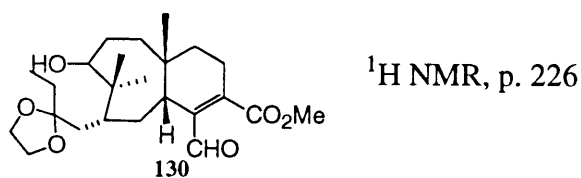
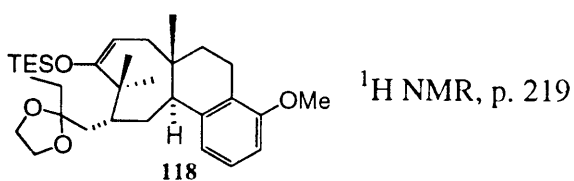
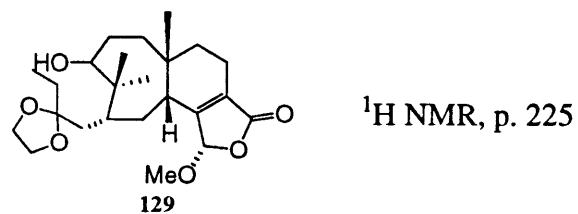
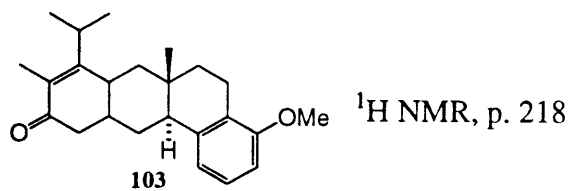
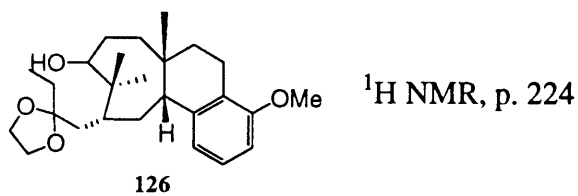
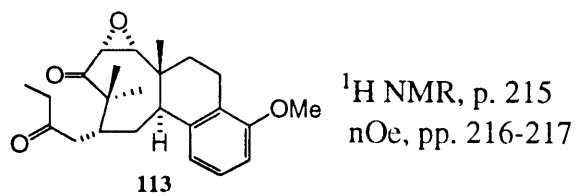
^1H NMR, p. 213

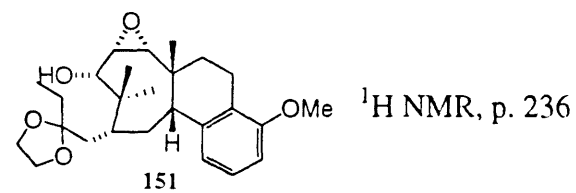
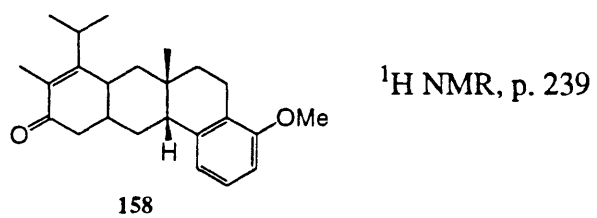
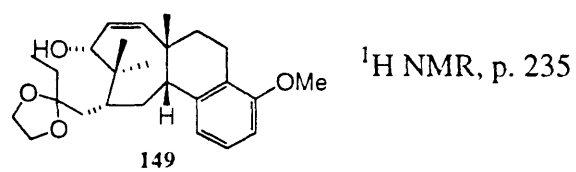
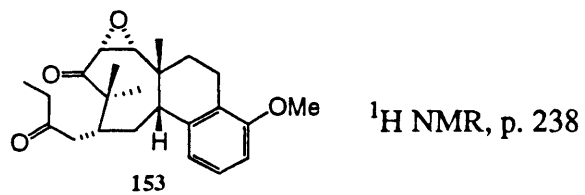
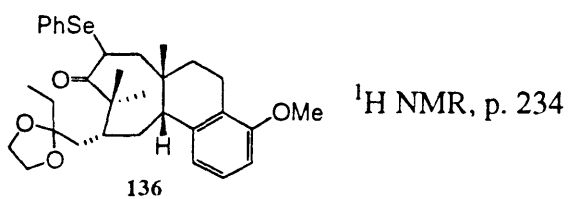
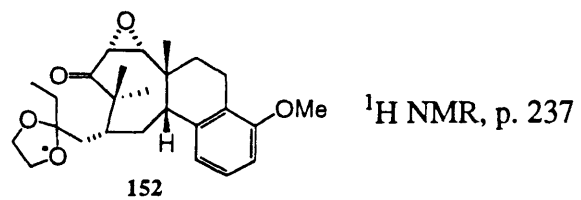
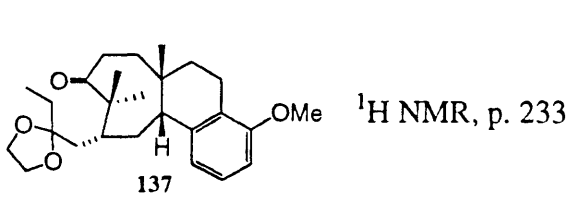


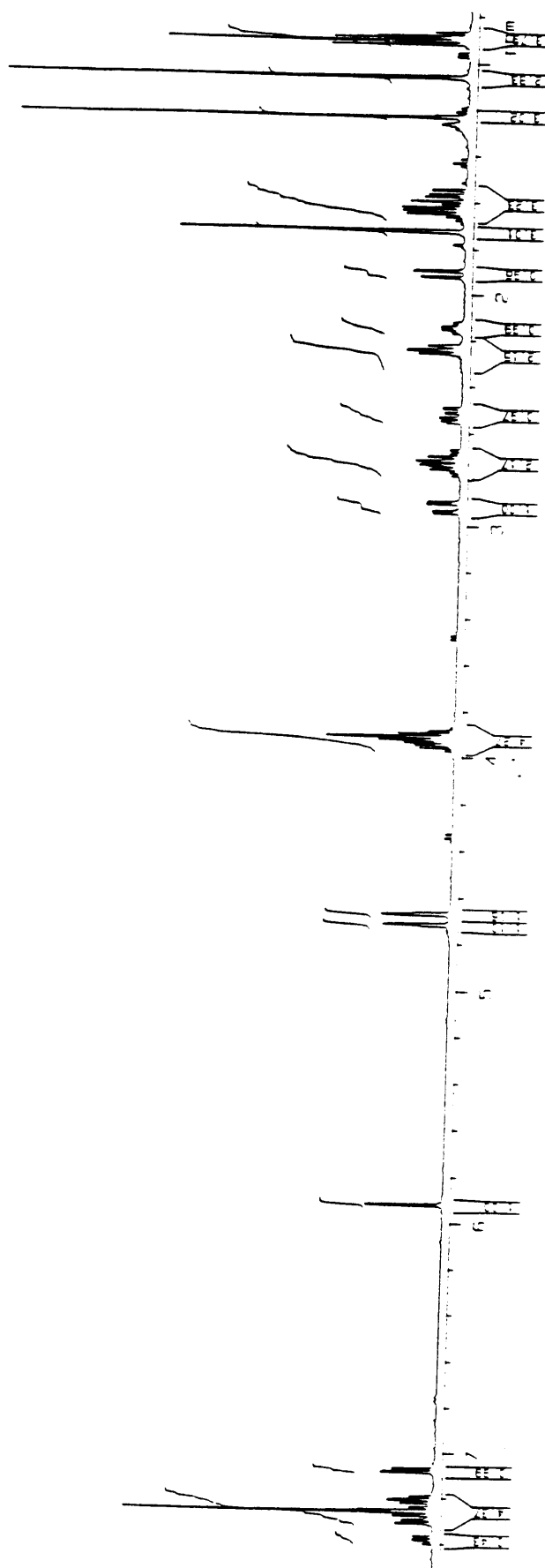
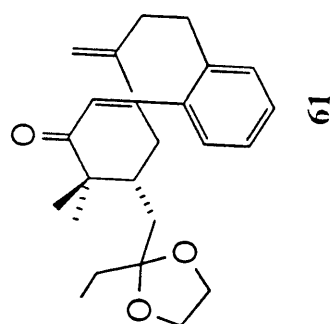
^1H NMR, p. 203

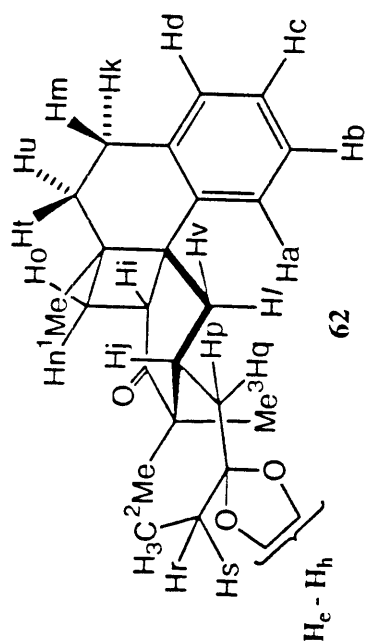


^1H NMR, p. 214

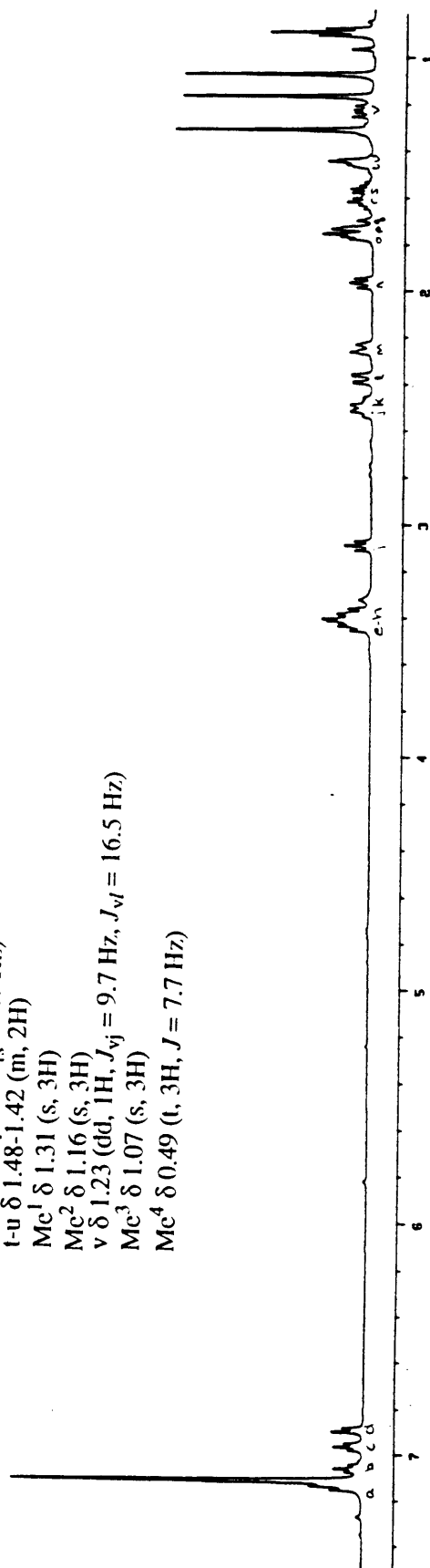


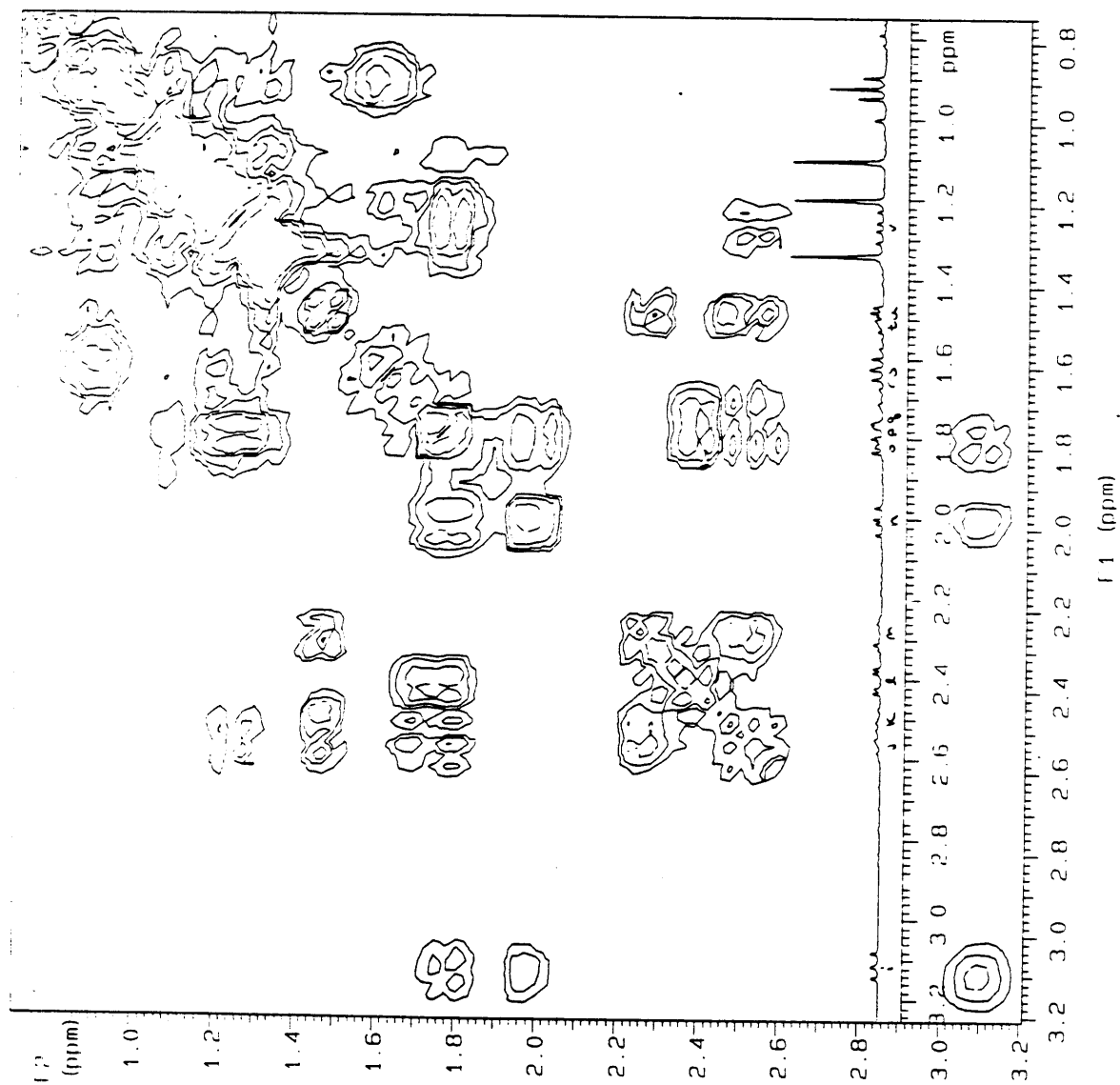


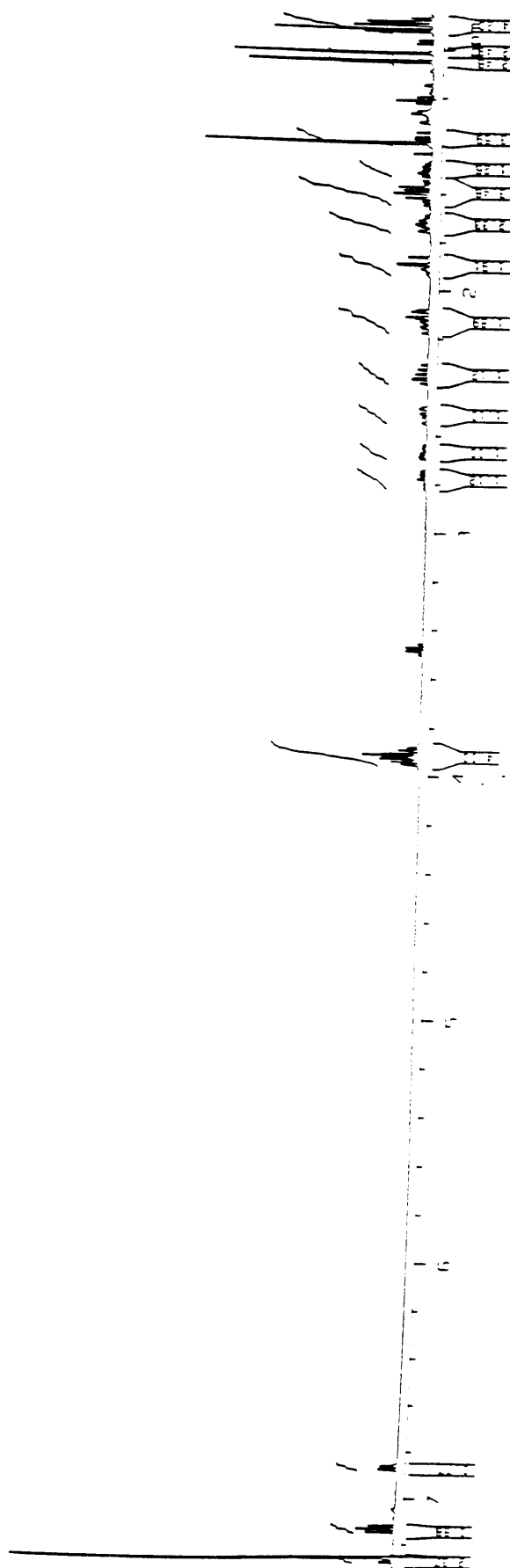
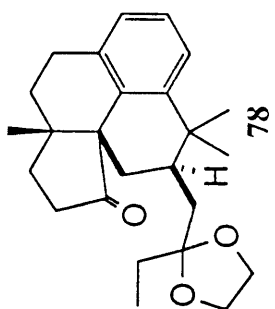


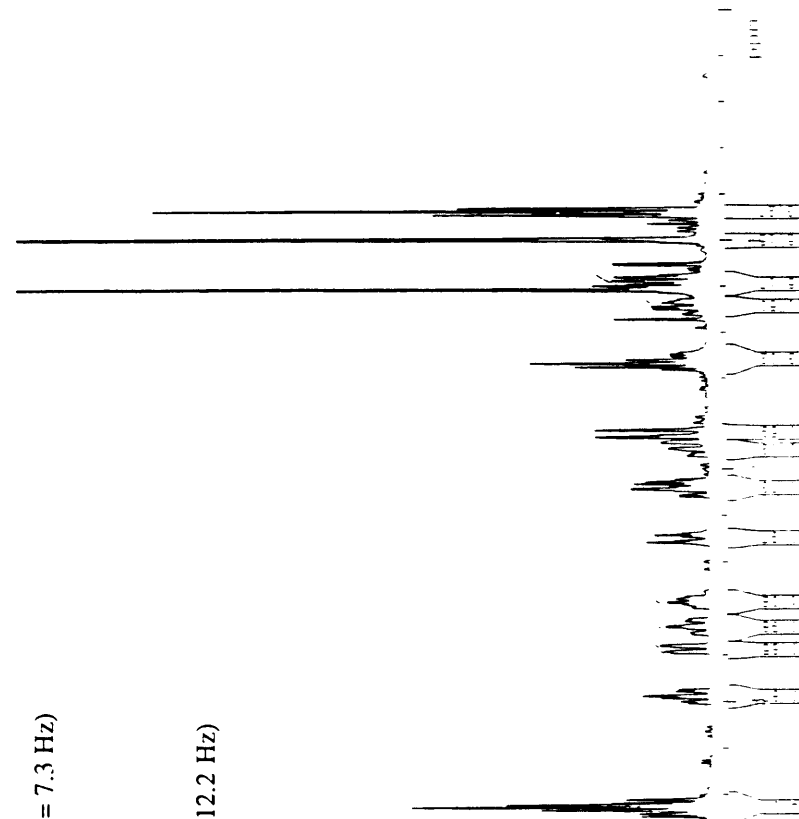


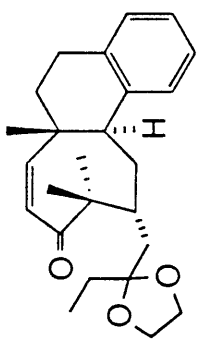
- a δ 7.14 (d, 1H, $J = 8.7$ Hz)
 b δ 7.06 (t, 1H, $J = 8.7$ Hz)
 c δ 6.96 (t, 1H, $J = 8.7$ Hz)
 d δ 6.89 (d, 1H, $J = 8.7$ Hz)
 e-h δ 3.49-3.37 (m, 4H, ketal)
 i δ 3.09 (dd, 1H, $J_{in} = 9.7$ Hz, $J_{io} = 11.0$)
 j δ 2.52-2.49 (m, 1H)
 k δ 2.49 (ddd, 1H, $J_{ku} = 6.5$ Hz, $J_{kt} = 11.6$ Hz, $J_{km} = 17.4$ Hz)
 l δ 2.37 (dd, 1H, $J_{jl} = 3.9$ Hz, $J_{vl} = 16.5$ Hz)
 m δ 2.24 (ddd, 1H, $J_{mt} = 3.9$ Hz, $J_{mu} = 3.9$ Hz, $J_{mk} = 17.4$ Hz)
 n δ 1.96 (dd, 1H, $J_{ni} = 9.7$ Hz, $J_{no} = 12.9$ Hz)
 o δ 1.75 (dd, 1H, $J_{oi} = 11.0$ Hz, $J_{on} = 12.9$ Hz)
 p-q δ 1.77-1.68 (m, 2H)
 r δ 1.64 (q, 1H, $J_{rs} = 7.7$ Hz)
 s δ 1.55 (q, 1H, $J_{rs} = 7.7$ Hz)
 t-u δ 1.48-1.42 (m, 2H)
 Me¹ δ 1.31 (s, 3H)
 Me² δ 1.16 (s, 3H)
 v δ 1.23 (dd, 1H, $J_{vj} = 9.7$ Hz, $J_{vl} = 16.5$ Hz)
 Me³ δ 1.07 (s, 3H)
 Me⁴ δ 0.49 (t, 3H, $J = 7.7$ Hz)



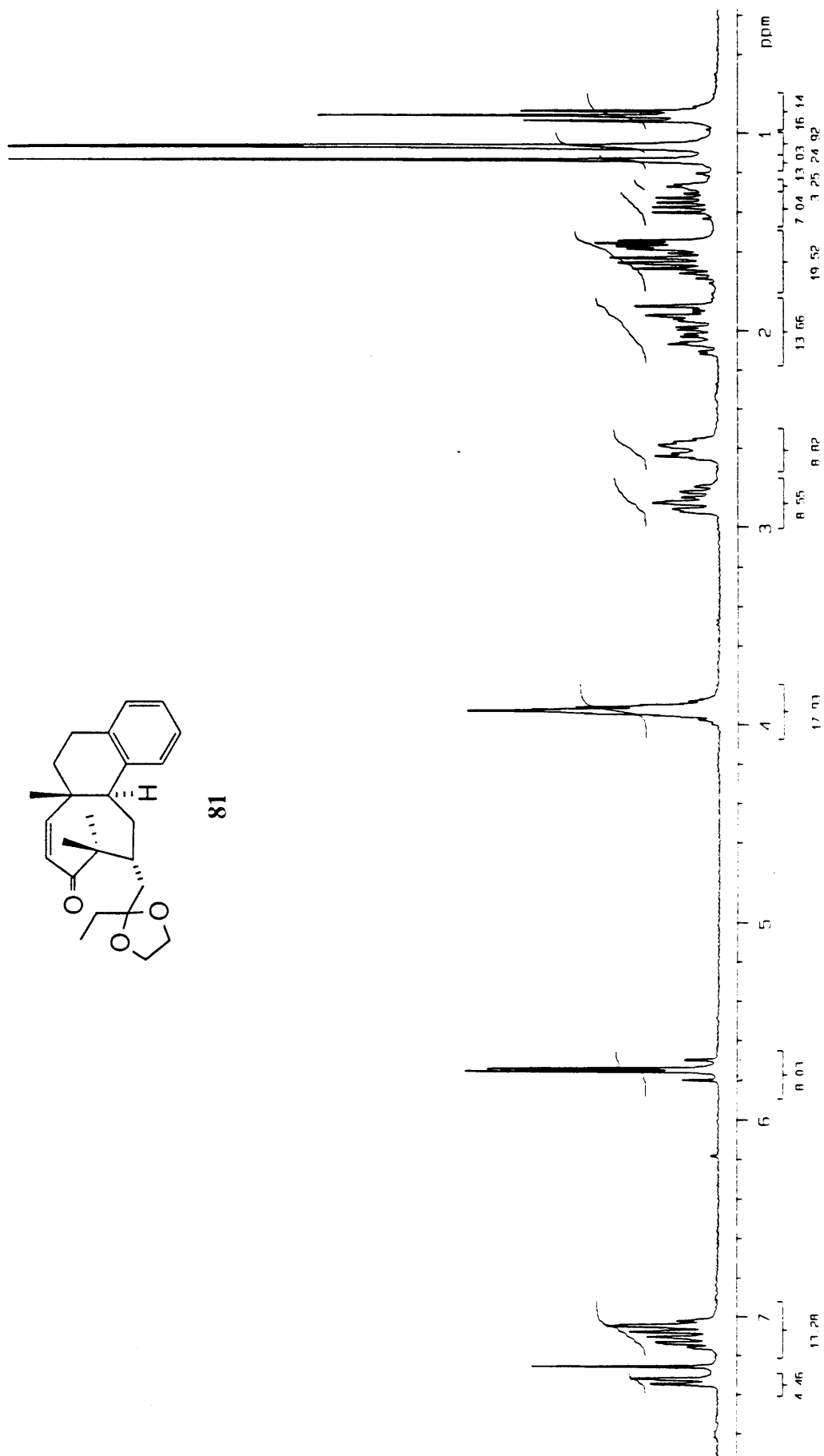


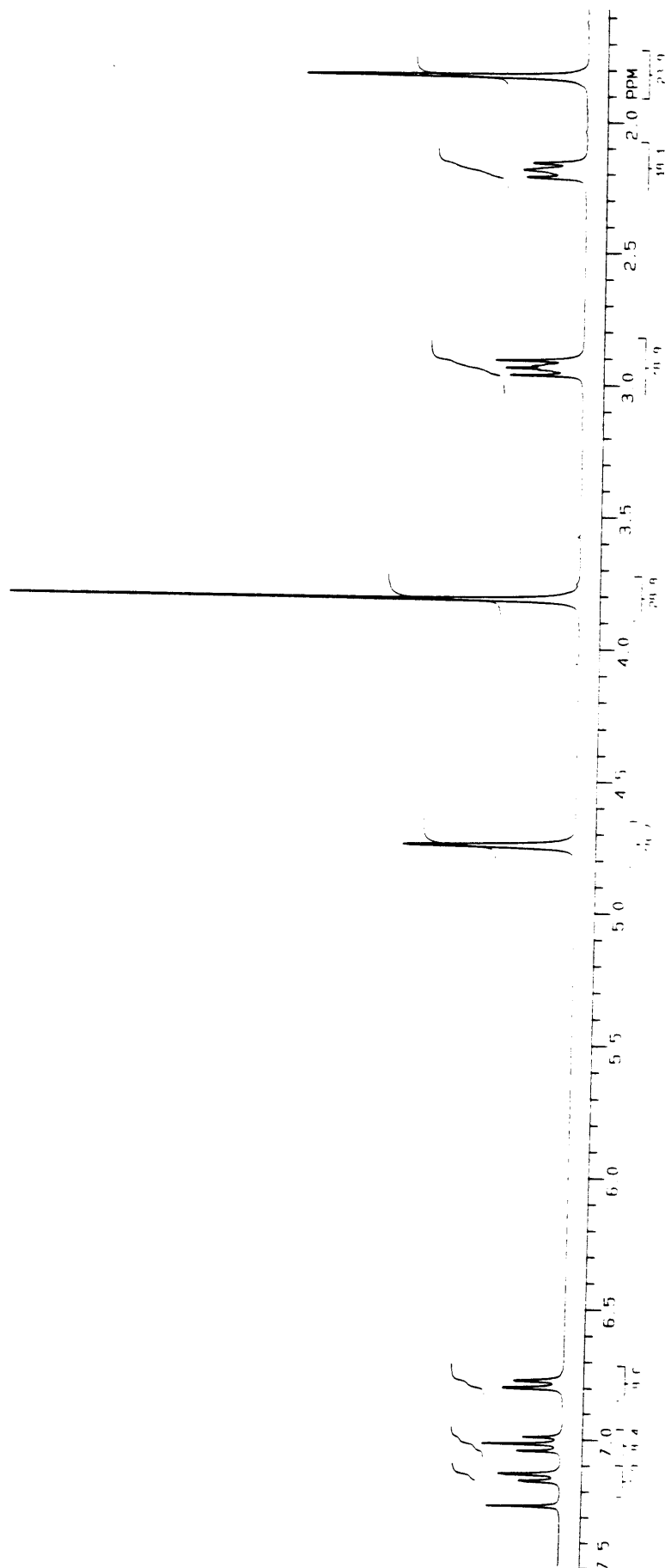
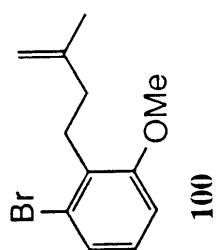


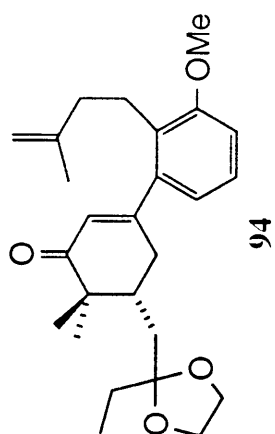


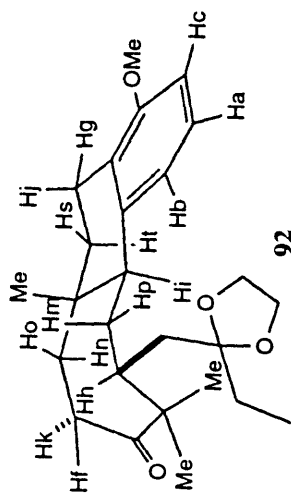


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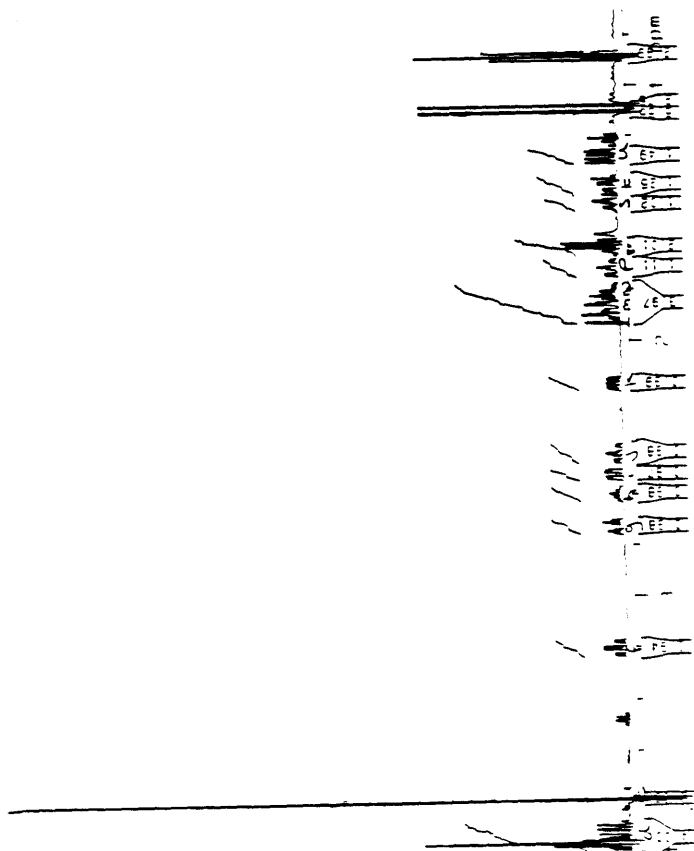


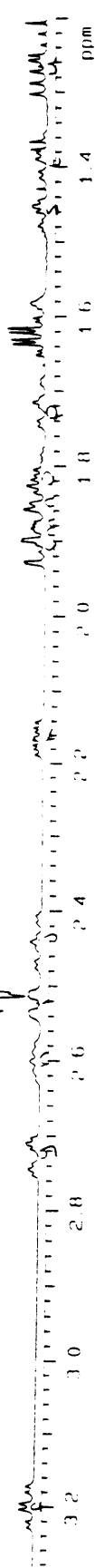
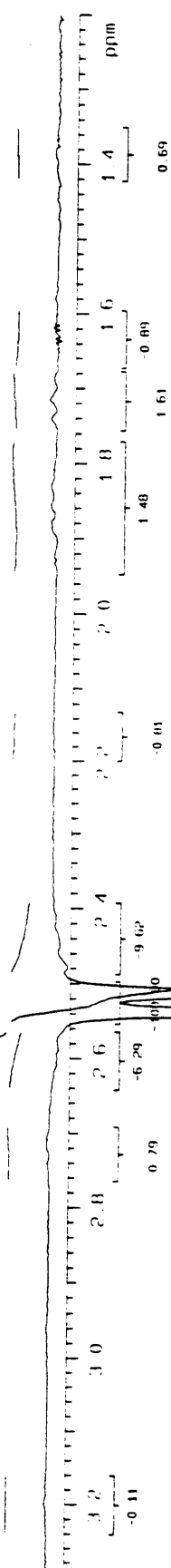
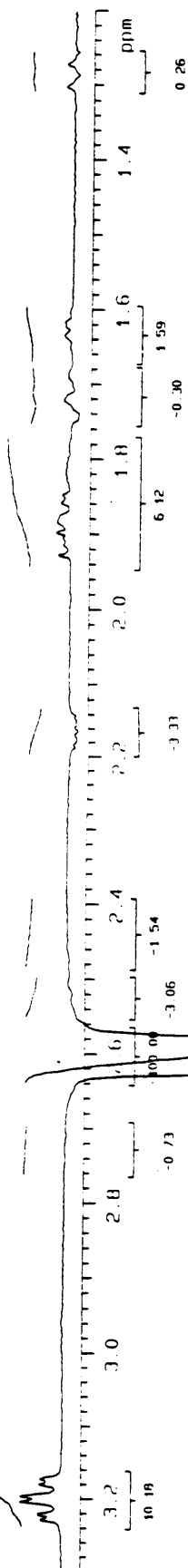
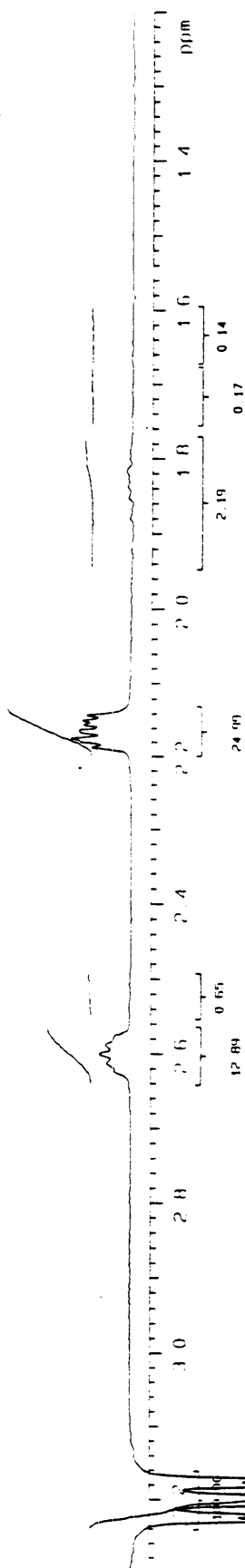


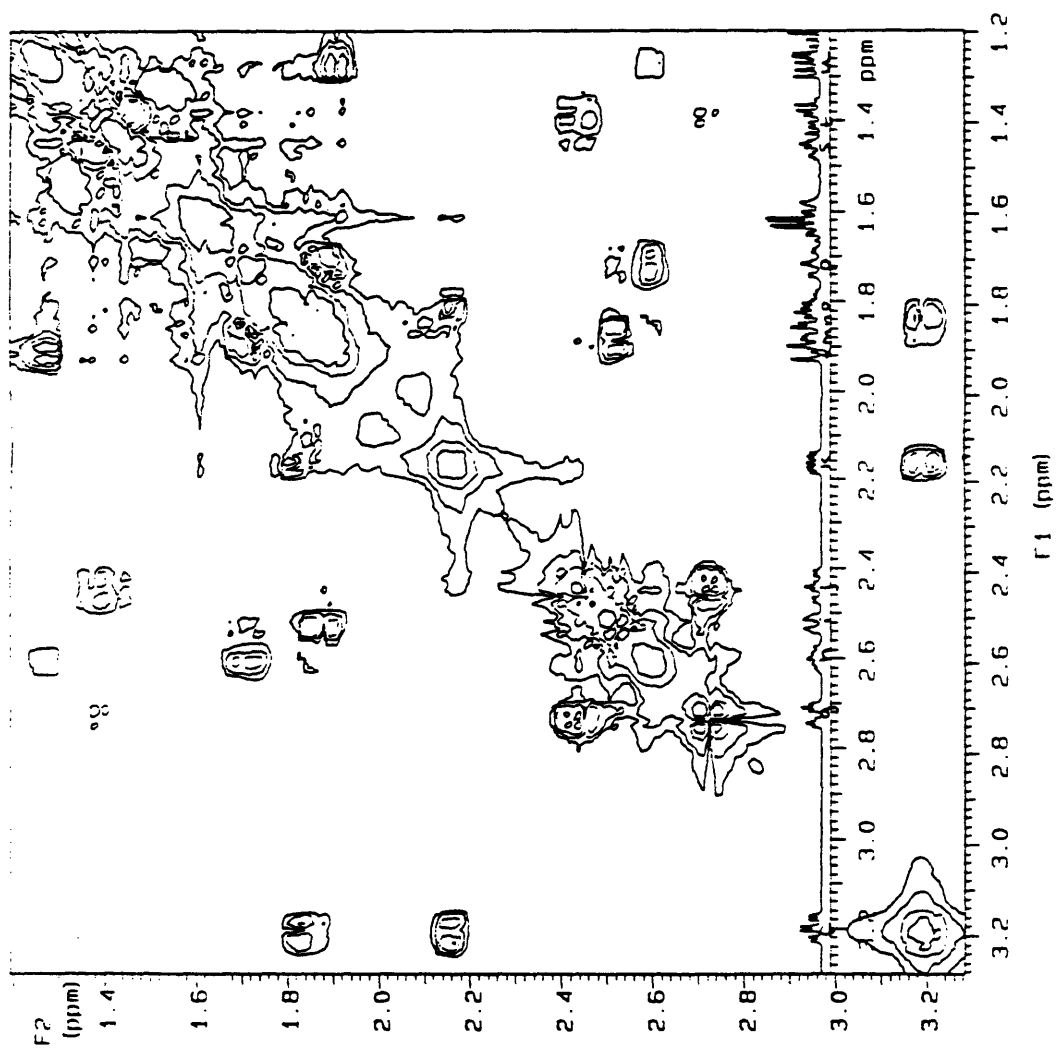


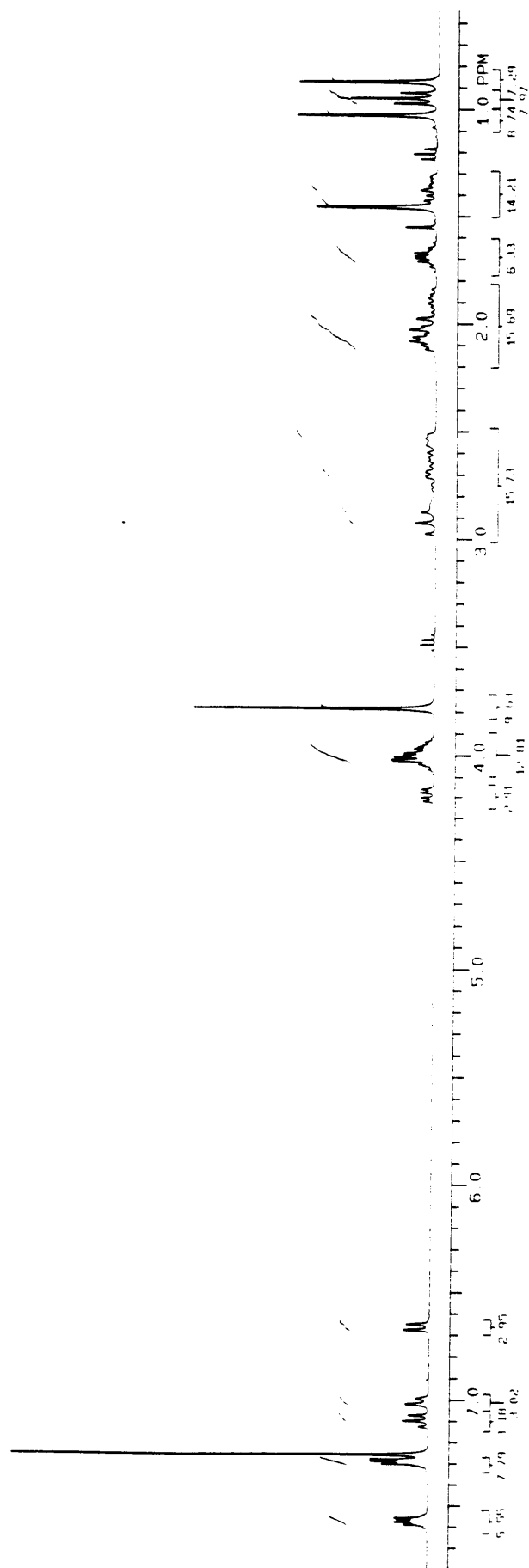
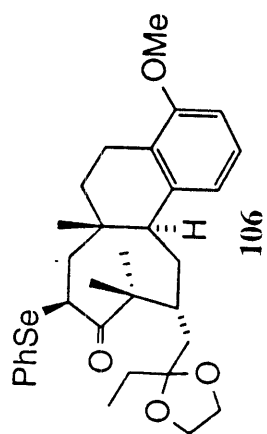


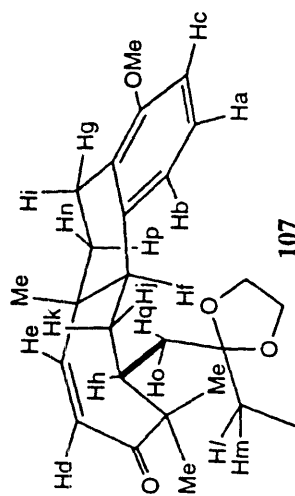
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 b δ 6.74 (d, 1H, $J = 7.8$ Hz)
 c δ 6.58 (d, 1H, $J = 7.8$ Hz)
 d δ 4.00-3.75 (m, 4H, ketal)
 e δ 3.74 (s, 3H, OMe)
 f δ 3.20 (ddd, 1H, $J_{fo} = 3.8$ Hz, $J_{fn} = 12.1$ Hz, $J_{fk} = 12.1$ Hz)
 g δ 2.73 (ddd, 1H, $J_{gs} = 3.6$ Hz, $J_{gt} = 3.6$ Hz, $J_{gj} = 17.0$ Hz)
 h δ 2.60 (dddd, 1H, $J_{hi} = 1.7$ Hz, $J_{hm} = 4.5$ Hz, $J_{hu} = 7.0$ Hz, $J_{hp} = 12.3$ Hz)
 i δ 2.53 (dd, 1H, $J_{ip} = 3.4$ Hz, $J_{im} = 12.8$ Hz)
 j δ 2.44 (ddd, 1H, $J_{js} = 4.5$ Hz, $J_{jt} = 13.0$ Hz, $J_{jg} = 17.0$ Hz)
 k δ 2.16 (ddd, 1H, $J_{kn} = 3.8$ Hz, $J_{ko} = 6.8$ Hz, $J_{kf} = 12.8$ Hz)
 l δ 1.91 (dd, 1H, $J_{lj} = 1.7$ Hz, $J_{lu} = 14.9$ Hz)
 m δ 1.89 (ddd, 1H, $J_{hm} = 4.5$ Hz, $J_{im} = 13.0$ Hz, $J_{mp} = 15.3$ Hz)
 n δ 1.83 (m, 1H)
 o δ 1.80 (ddd, 1H, $J_{fo} = 3.8$ Hz, $J_{ko} = 6.8$ Hz, $J_{no} = 14$ Hz)
 p δ 1.71 (ddd, 1H, $J_{pi} = 3.4$ Hz, $J_{hp} = 12.3$ Hz, $J_{mp} = 15.3$ Hz)
 pq δ 1.63 ($J = 7.7$ Hz)
 s δ 1.48 (ddd, 1H, $J_{gs} = 2.9$ Hz, $J_{js} = 4.4$ Hz, $J_{st} = 12.9$ Hz)
 t δ 1.39 (ddd, 1H, $J_{gt} = 4.3$ Hz, $J_{jt} = 12.9$ Hz, $J_{st} = 12.9$ Hz)
 u δ 1.29 (dd, 1H, $J_{hu} = 7.2$ Hz, $J_{lu} = 14.9$ Hz)





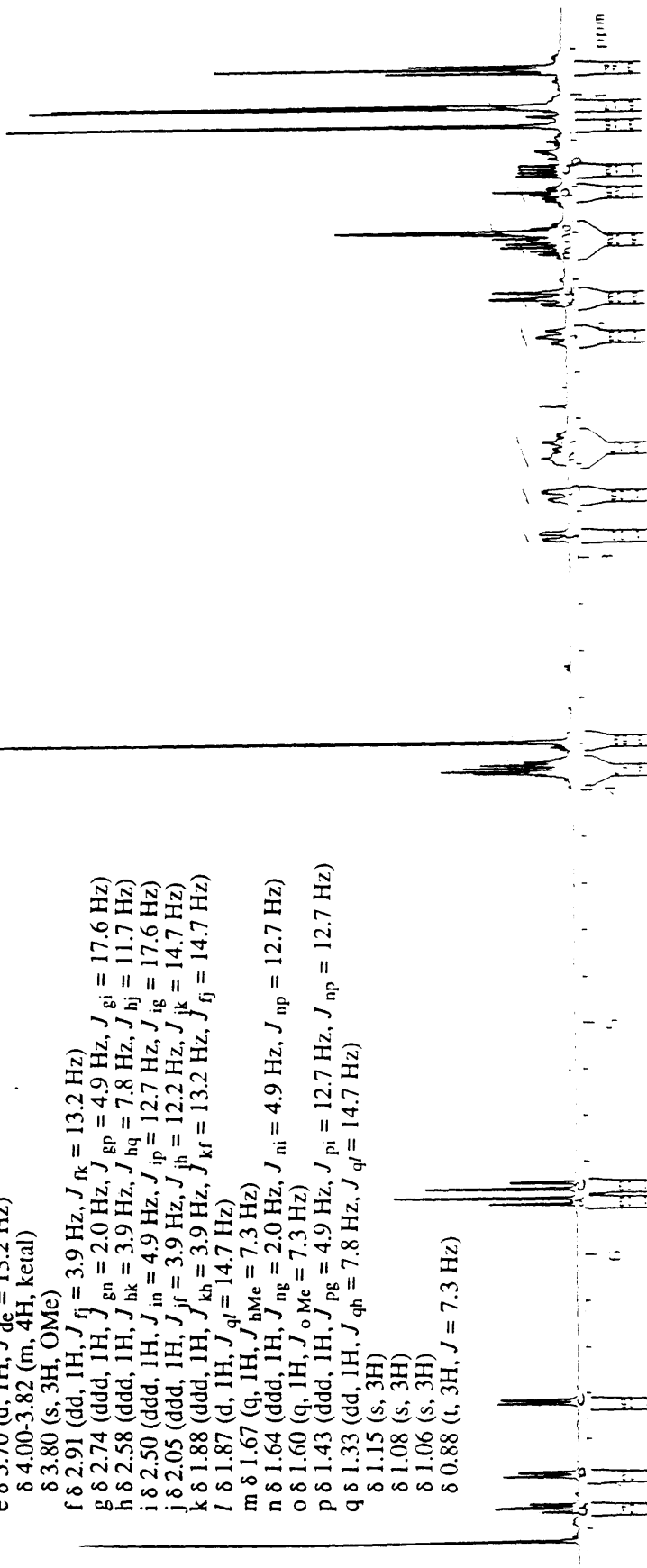


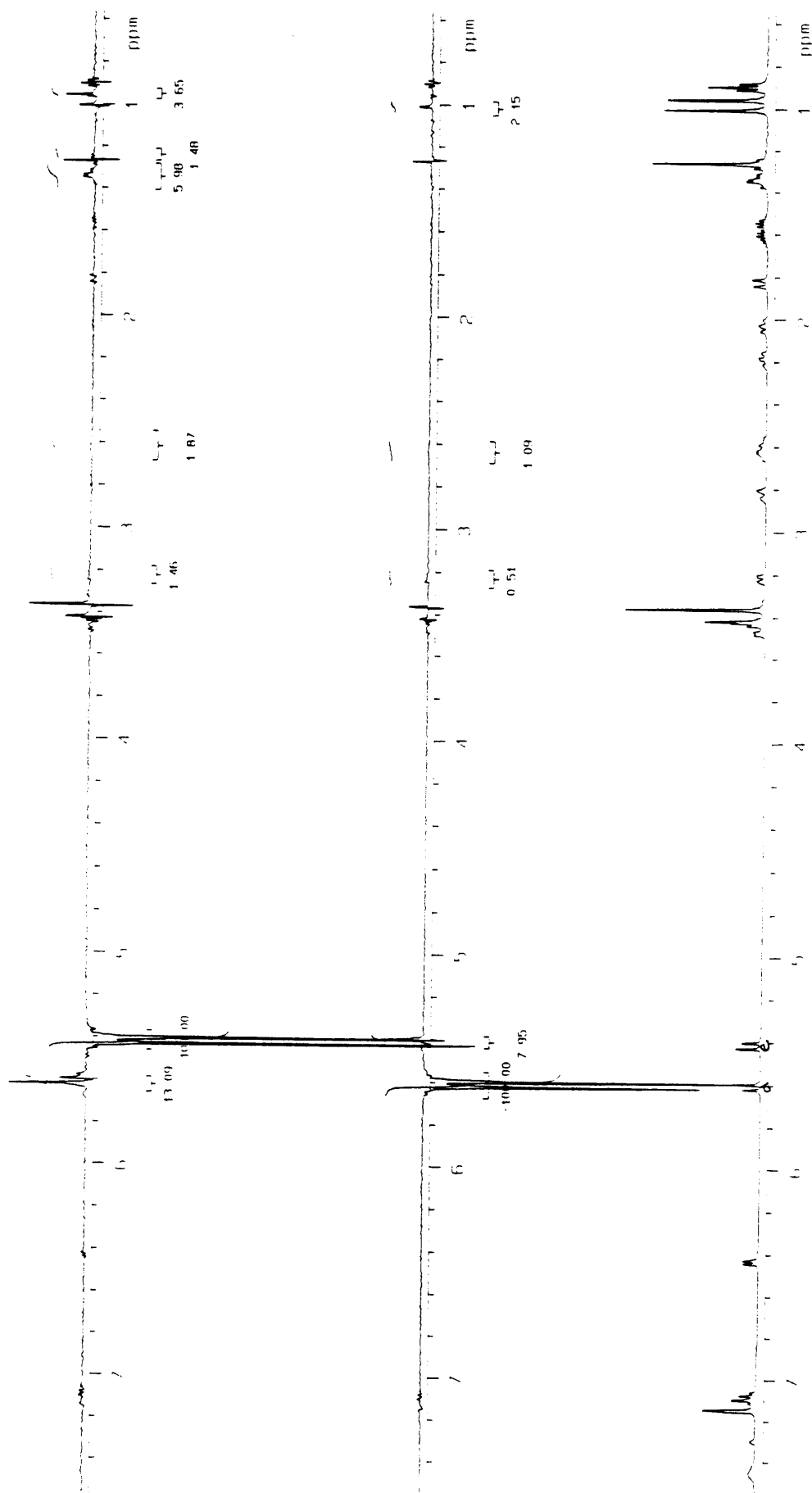


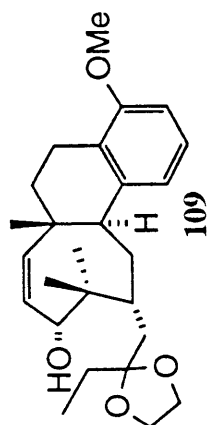


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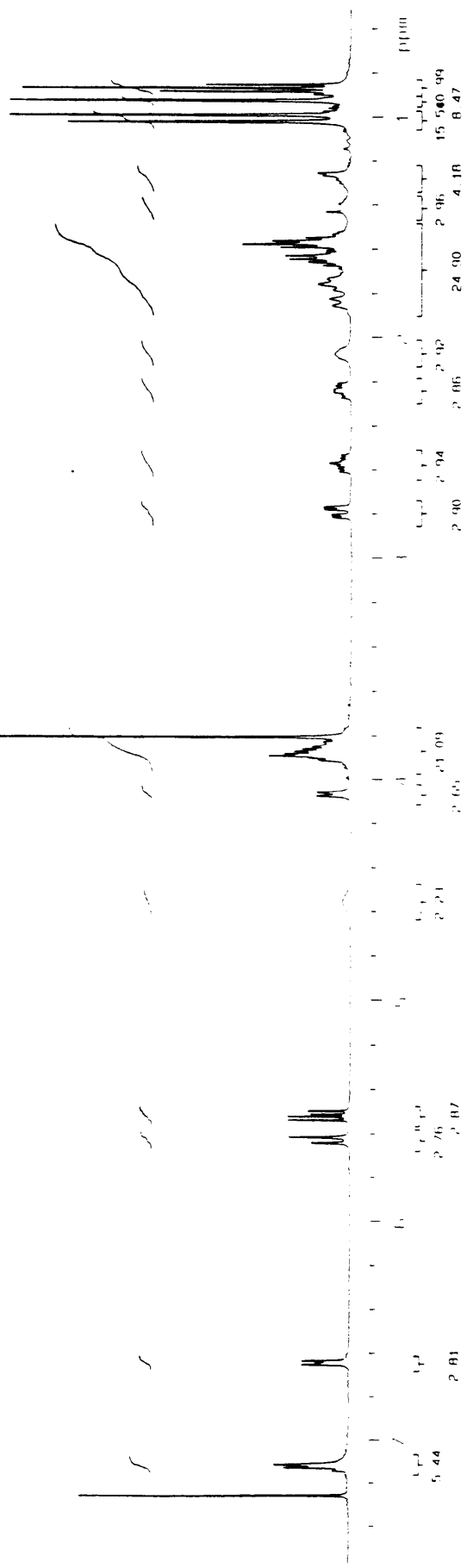
- a δ 7.10 (t, 1H, $J = 7.8$ Hz)
b δ 6.96 (d, 1H, $J = 7.8$ Hz)
c δ 6.64 (d, 1H, $J = 7.8$ Hz)
d δ 5.77 (d, 1H, $J_{de} = 13.2$ Hz)
e δ 5.70 (d, 1H, $J_{de} = 13.2$ Hz)
 δ 4.00-3.82 (m, 4H, ketal)
 δ 3.80 (s, 3H, OMe)
f δ 2.91 (dd, 1H, $J_{fg} = 3.9$ Hz, $J_{fh} = 13.2$ Hz)
g δ 2.74 (ddd, 1H, $J_{gn} = 2.0$ Hz, $J_{gp} = 4.9$ Hz, $J_{gi} = 17.6$ Hz)
h δ 2.58 (ddd, 1H, $J_{hk} = 3.9$ Hz, $J_{hq} = 7.8$ Hz, $J_{hj} = 11.7$ Hz)
i δ 2.50 (ddd, 1H, $J_{in} = 4.9$ Hz, $J_{ip} = 12.7$ Hz, $J_{ig} = 17.6$ Hz)
j δ 2.05 (ddd, 1H, $J_{jr} = 3.9$ Hz, $J_{jh} = 12.2$ Hz, $J_{jk} = 14.7$ Hz)
k δ 1.88 (ddd, 1H, $J_{kh} = 3.9$ Hz, $J_{kf} = 13.2$ Hz, $J_{kj} = 14.7$ Hz)
l δ 1.87 (d, 1H, $J_{ql} = 14.7$ Hz)
m δ 1.67 (q, 1H, $J_{bm} = 7.3$ Hz)
n δ 1.64 (ddd, 1H, $J_{ng} = 2.0$ Hz, $J_{ni} = 4.9$ Hz, $J_{np} = 12.7$ Hz)
o δ 1.60 (q, 1H, $J_{om} = 7.3$ Hz)
p δ 1.43 (ddd, 1H, $J_{pg} = 4.9$ Hz, $J_{pi} = 12.7$ Hz, $J_{pp} = 12.7$ Hz)
q δ 1.33 (dd, 1H, $J_{qh} = 7.8$ Hz, $J_{ql} = 14.7$ Hz)
 δ 1.15 (s, 3H)
 δ 1.08 (s, 3H)
 δ 1.06 (s, 3H)
 δ 0.88 (t, 3H, $J = 7.3$ Hz)



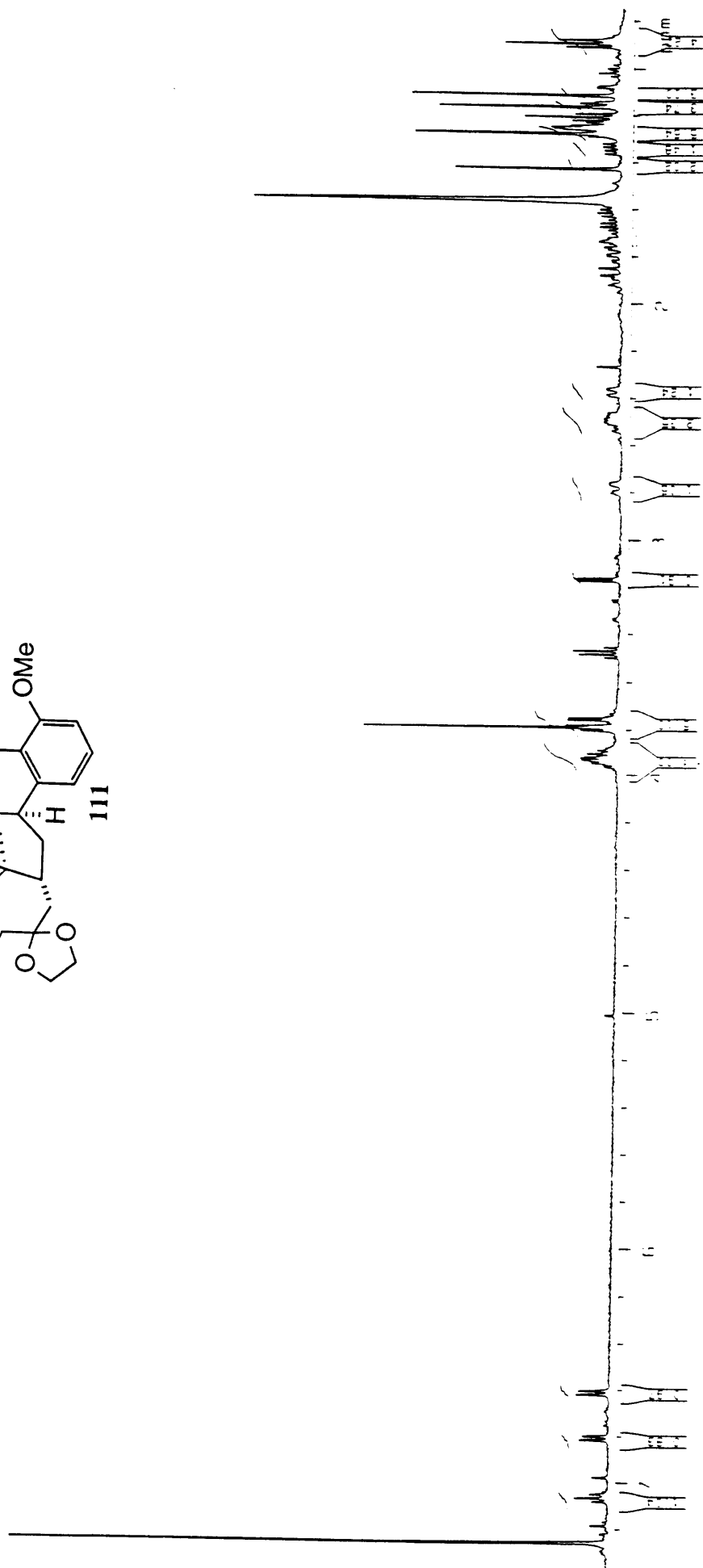
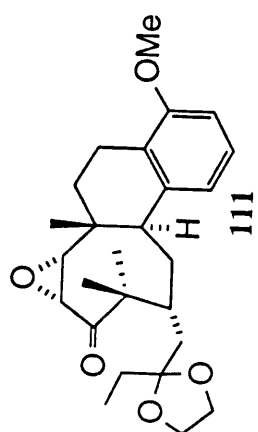


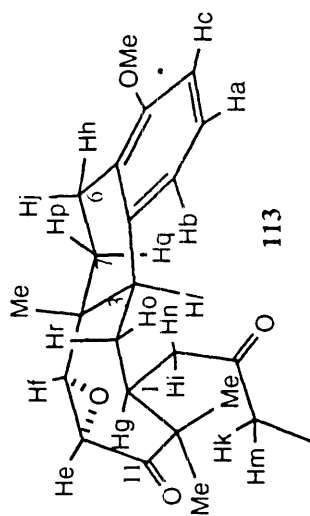


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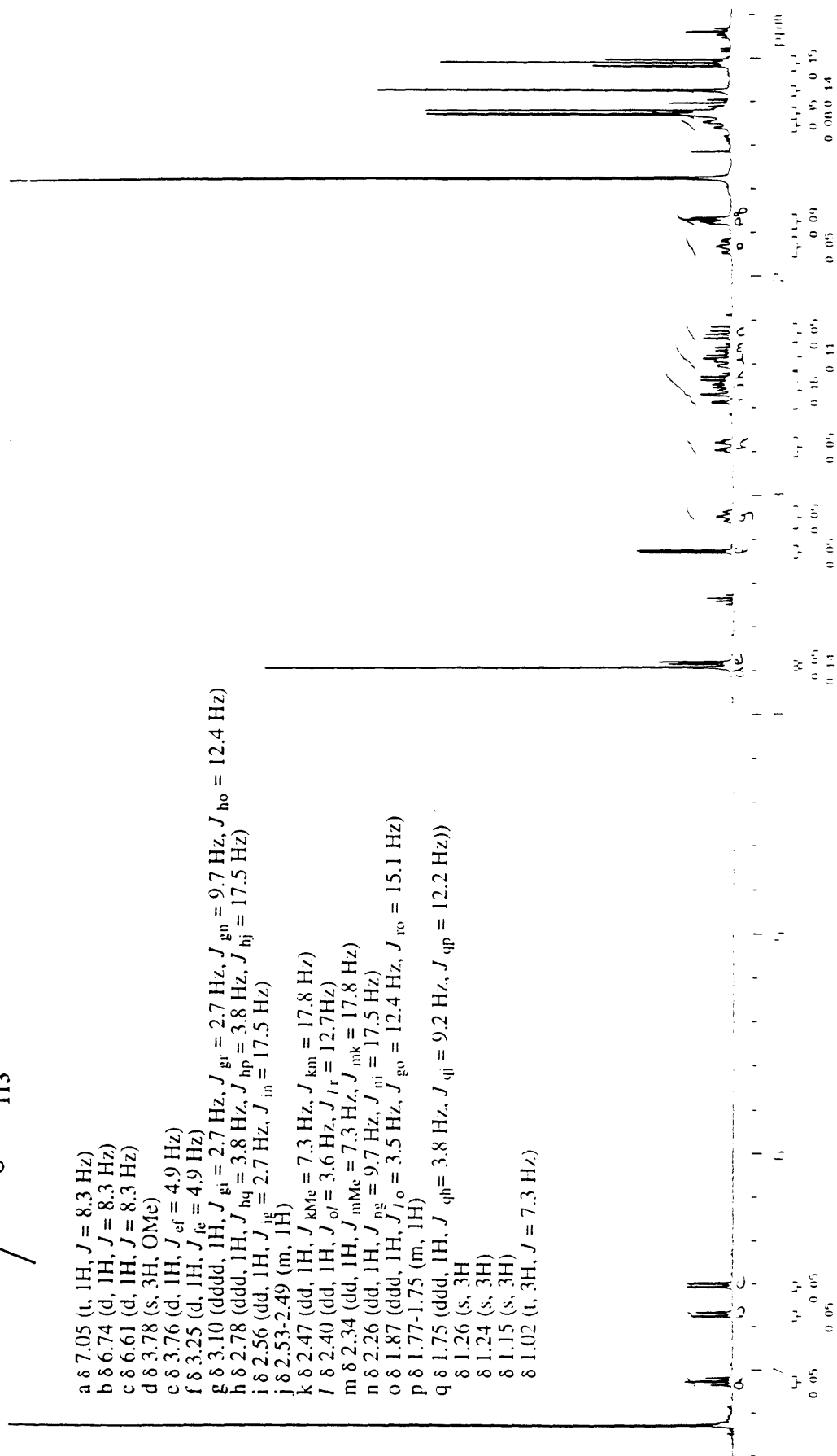




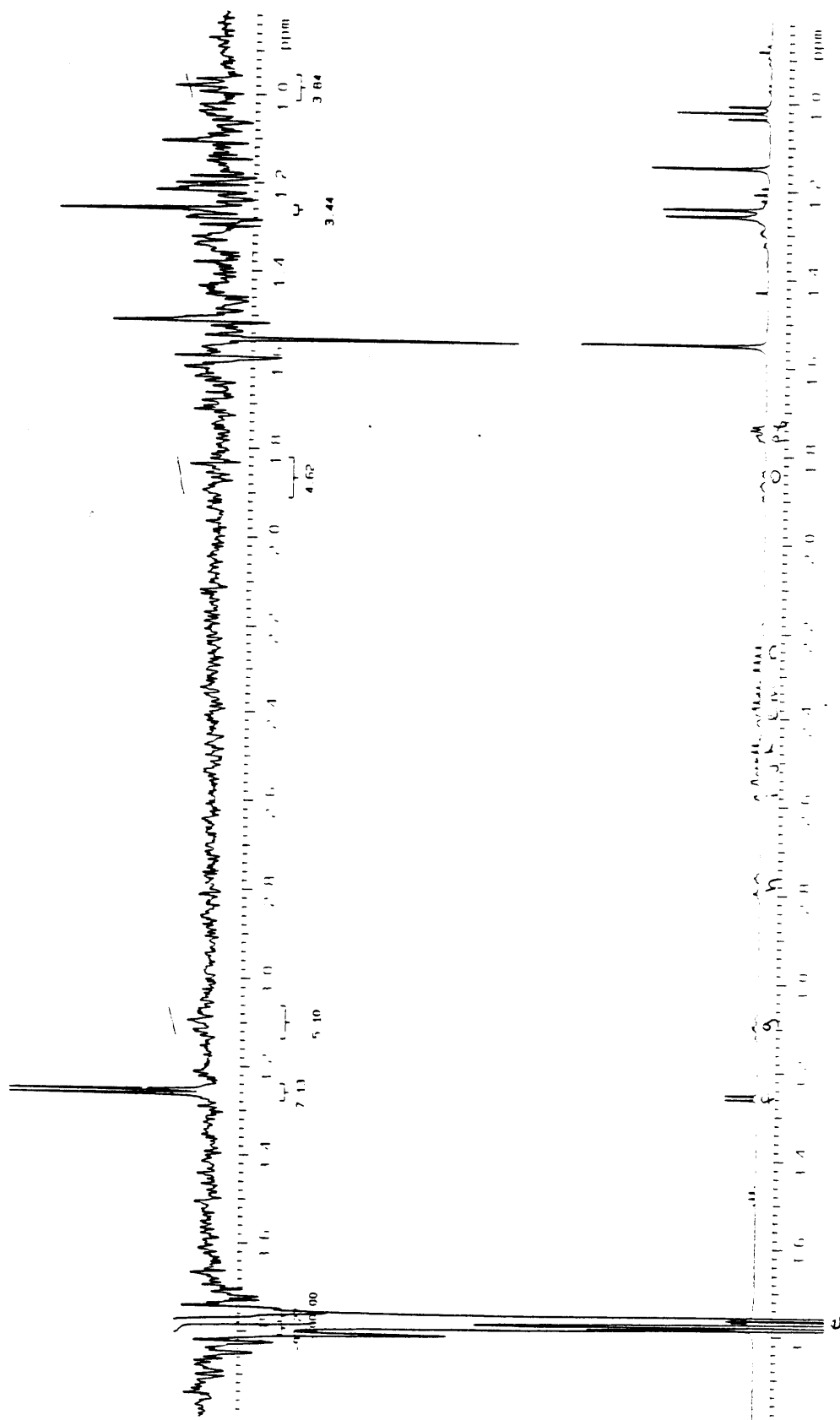


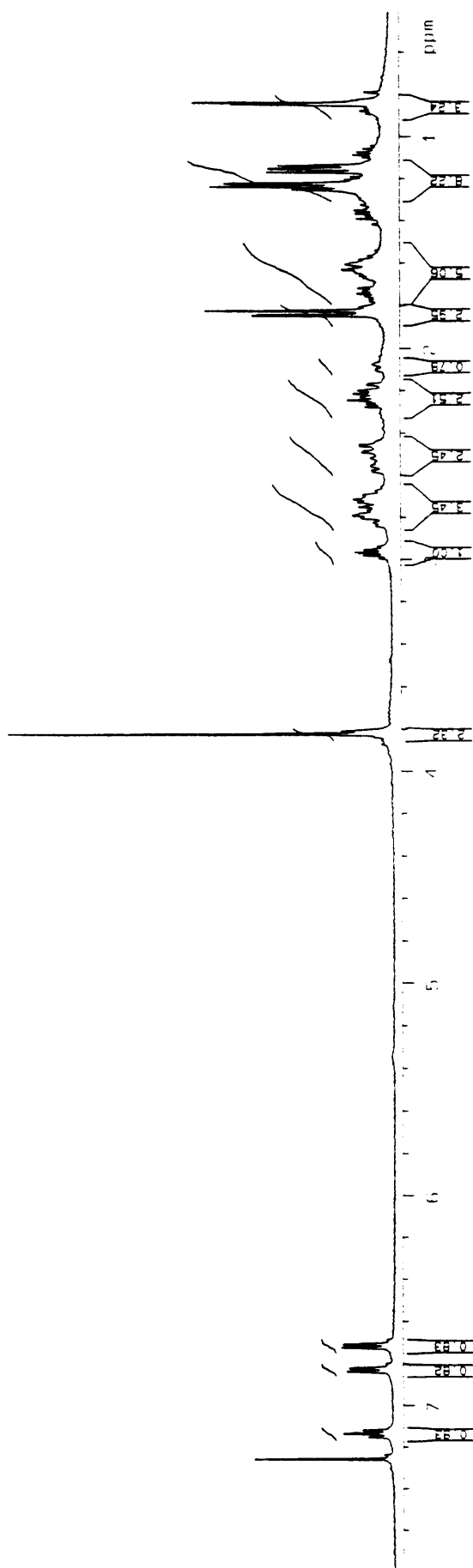
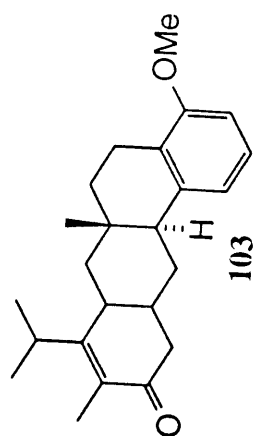


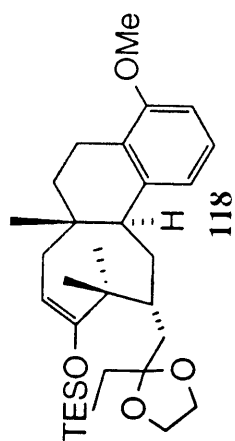
- a δ 7.05 (t, 1H, $J = 8.3$ Hz)
b δ 6.74 (d, 1H, $J = 8.3$ Hz)
c δ 6.61 (d, 1H, $J = 8.3$ Hz)
d δ 3.78 (s, 3H, OMe)
e δ 3.76 (d, 1H, $J_{ef} = 4.9$ Hz)
f δ 3.25 (d, 1H, $J_{fe} = 4.9$ Hz)
g δ 3.10 (dddd, 1H, $J_{gr} = 2.7$ Hz, $J_{gr} = 2.7$ Hz, $J_{gn} = 9.7$ Hz, $J_{ho} = 12.4$ Hz)
h δ 2.78 (ddd, 1H, $J_{hq} = 3.8$ Hz, $J_{hp} = 3.8$ Hz, $J_{hj} = 17.5$ Hz)
i δ 2.56 (dd, 1H, $J_{ig} = 2.7$ Hz, $J_{in} = 17.5$ Hz)
j δ 2.53-2.49 (m, 1H)
k δ 2.47 (dd, 1H, $J_{kMe} = 7.3$ Hz, $J_{km} = 17.8$ Hz)
l δ 2.40 (dd, 1H, $J_{ol} = 3.6$ Hz, $J_{lr} = 12.7$ Hz)
m δ 2.34 (dd, 1H, $J_{mMe} = 7.3$ Hz, $J_{mk} = 17.8$ Hz)
n δ 2.26 (dd, 1H, $J_{ng} = 9.7$ Hz, $J_{ni} = 17.5$ Hz)
o δ 1.87 (ddd, 1H, $J_{lo} = 3.5$ Hz, $J_{go} = 12.4$ Hz, $J_{ro} = 15.1$ Hz)
p δ 1.77-1.75 (m, 1H)
q δ 1.75 (ddd, 1H, $J_{qh} = 3.8$ Hz, $J_{qi} = 9.2$ Hz, $J_{qp} = 12.2$ Hz))
r δ 1.26 (s, 3H)
s δ 1.24 (s, 3H)
t δ 1.15 (s, 3H)
u δ 1.02 (t, 3H, $J = 7.3$ Hz)



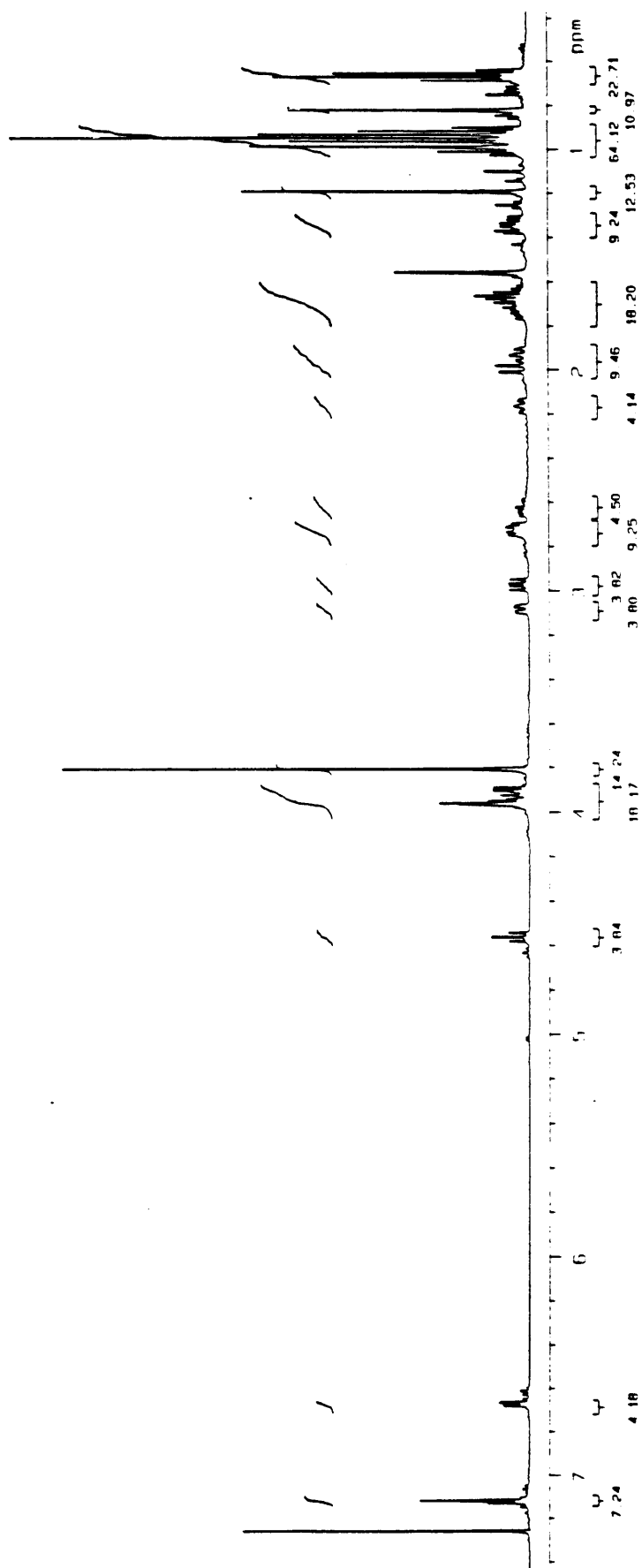




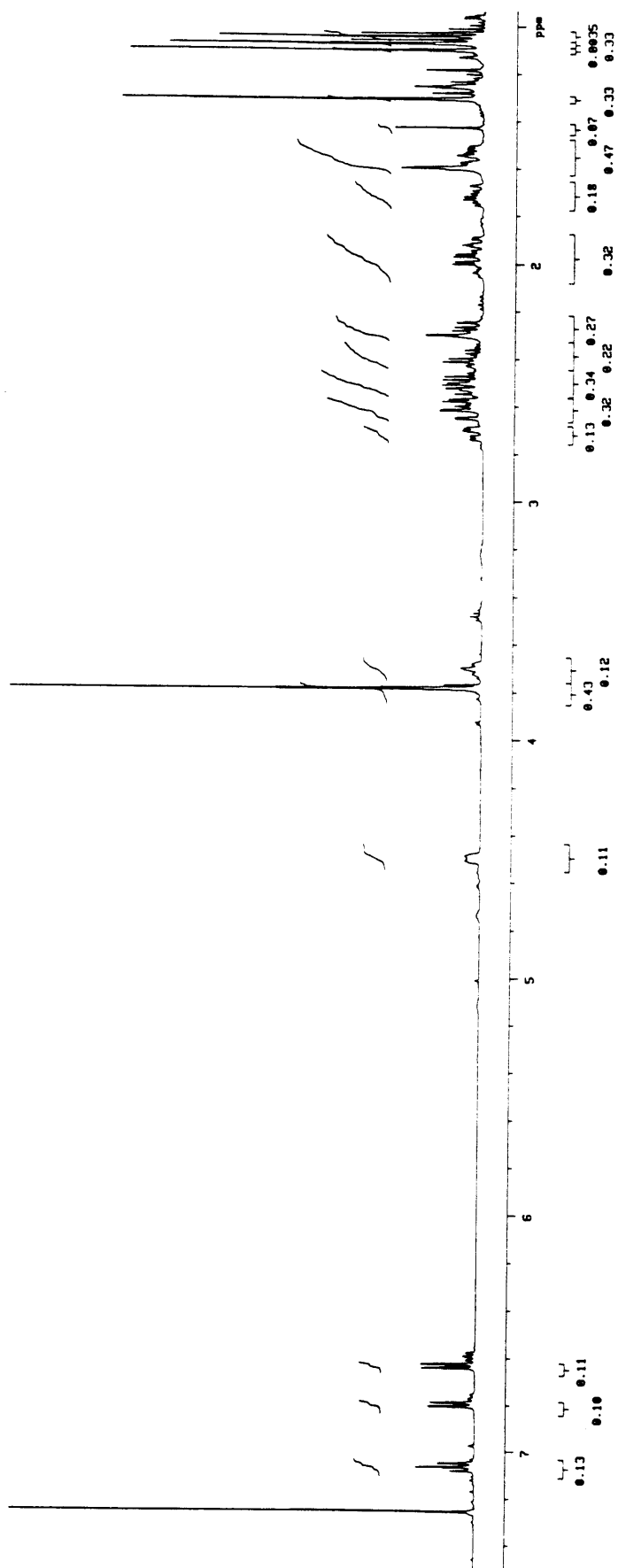
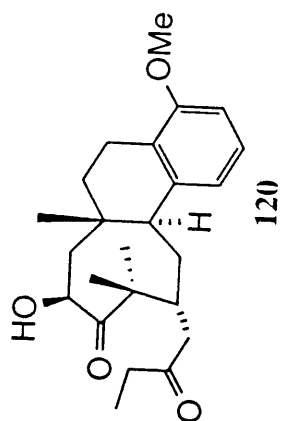


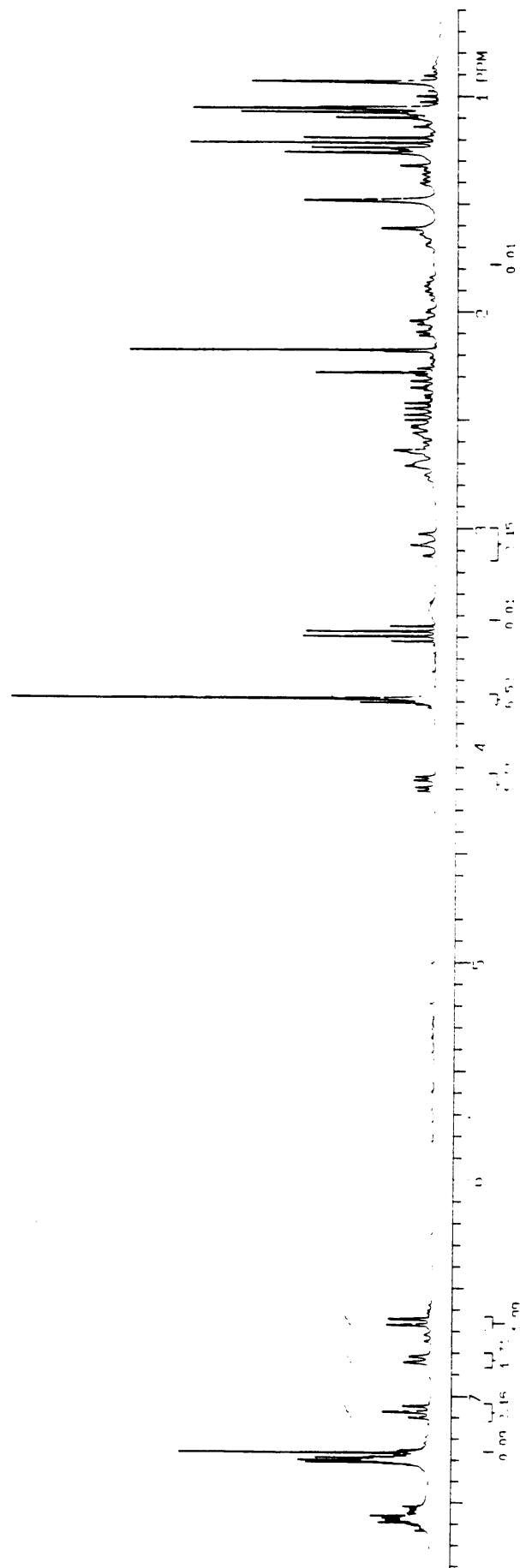
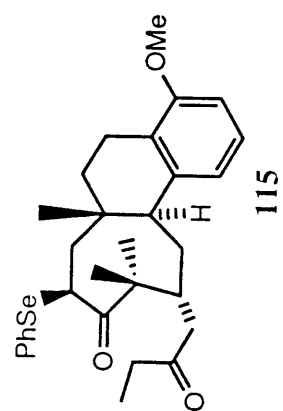


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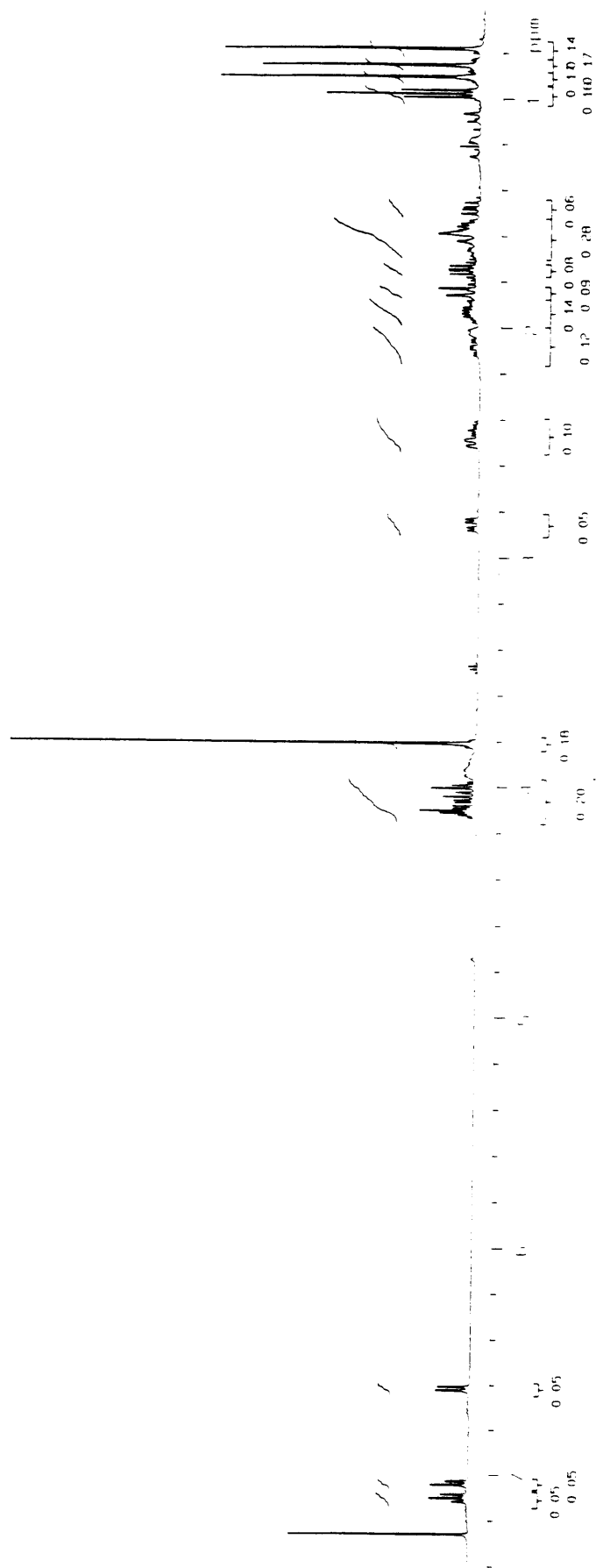
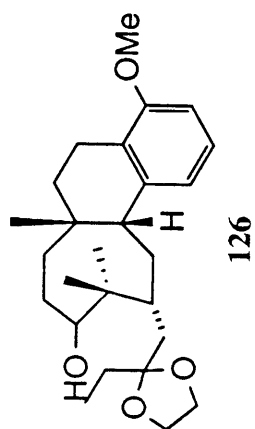


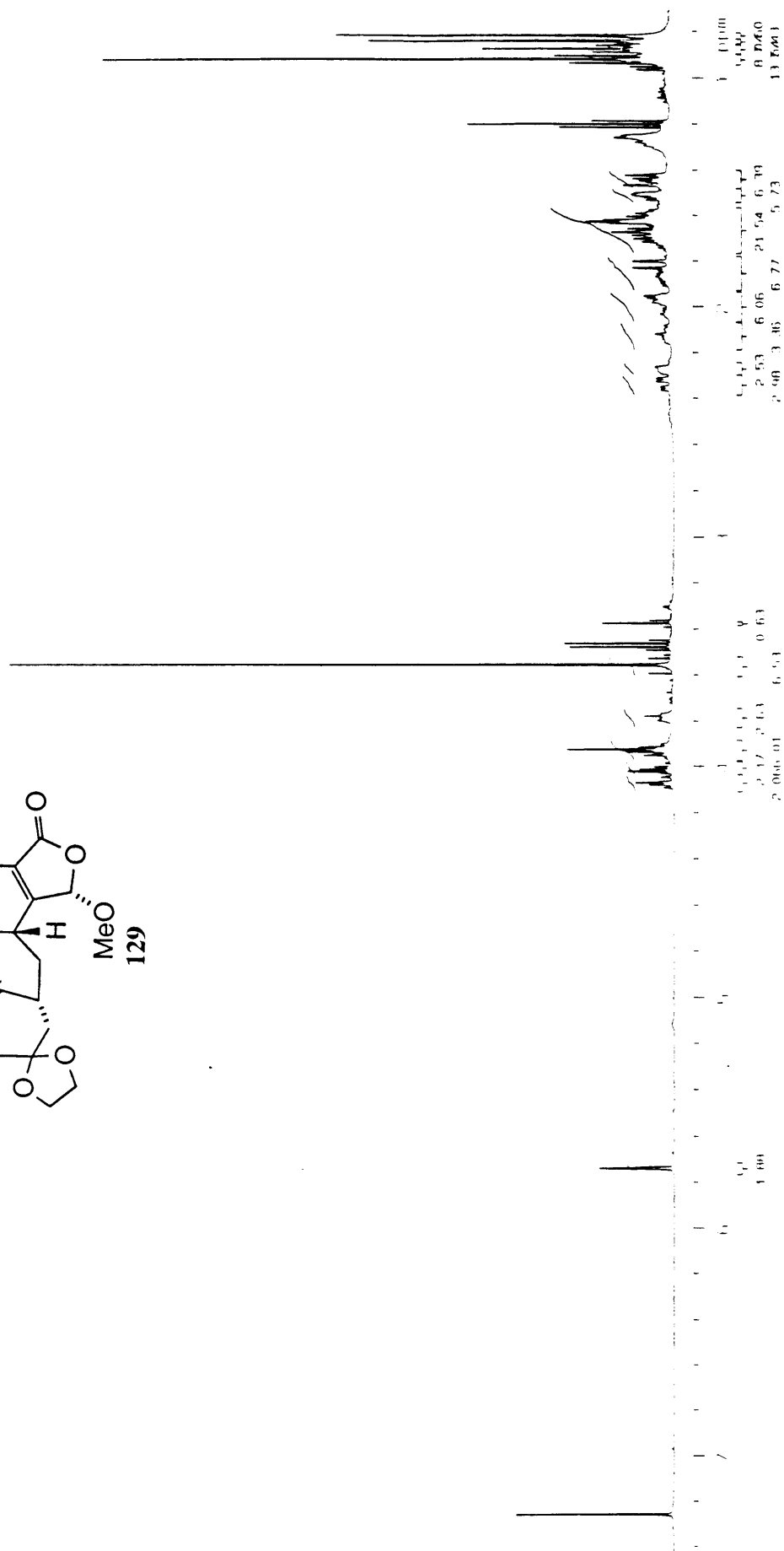
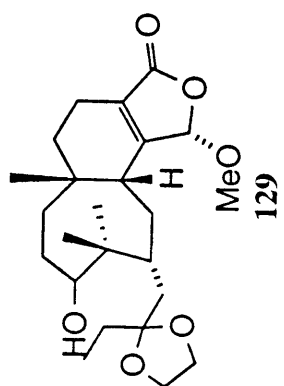


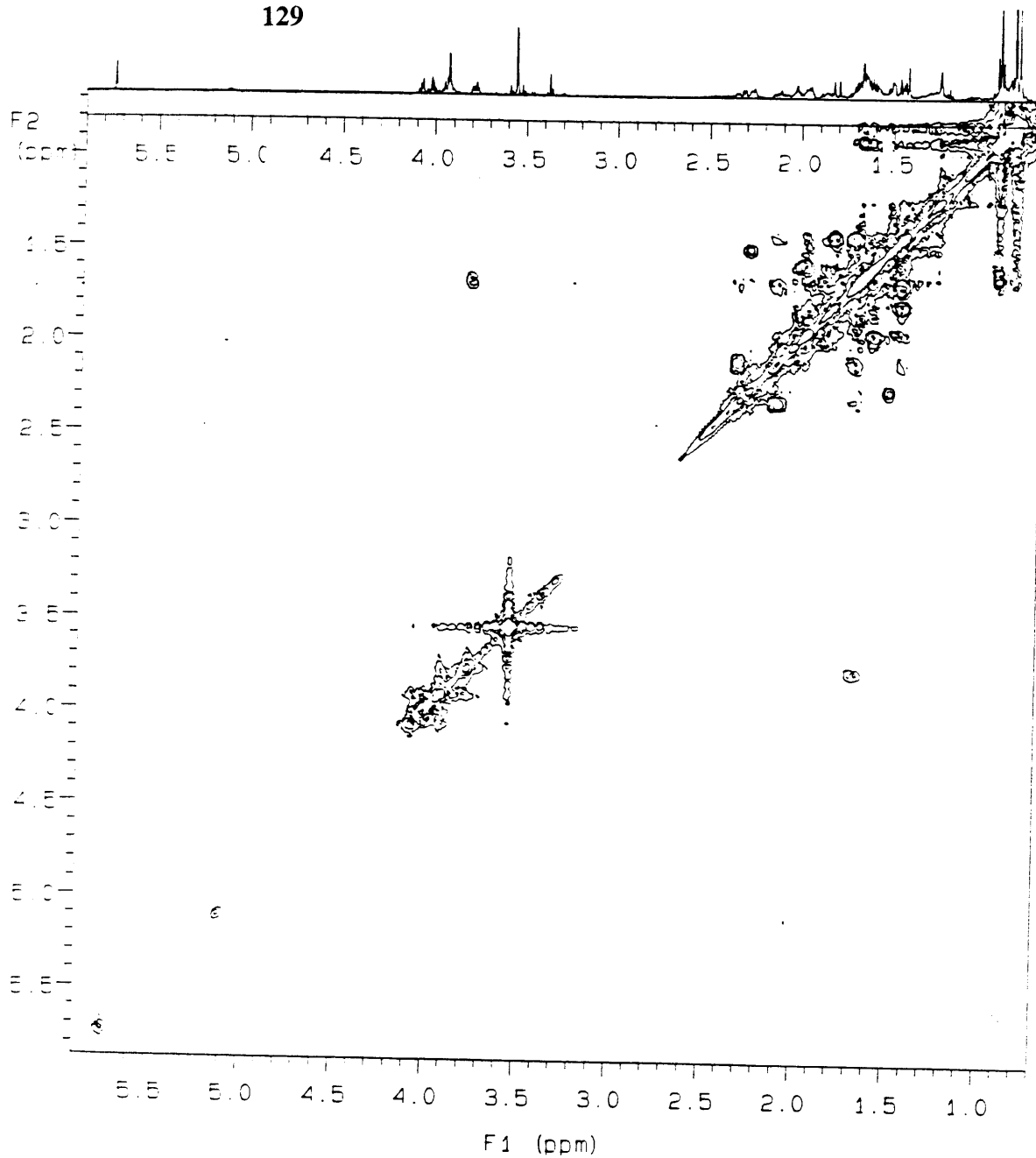
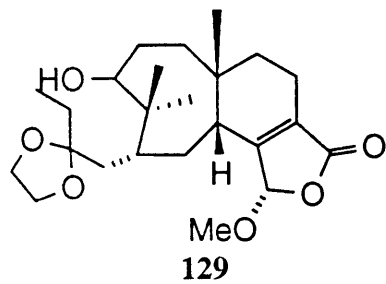


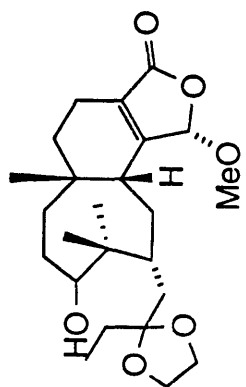




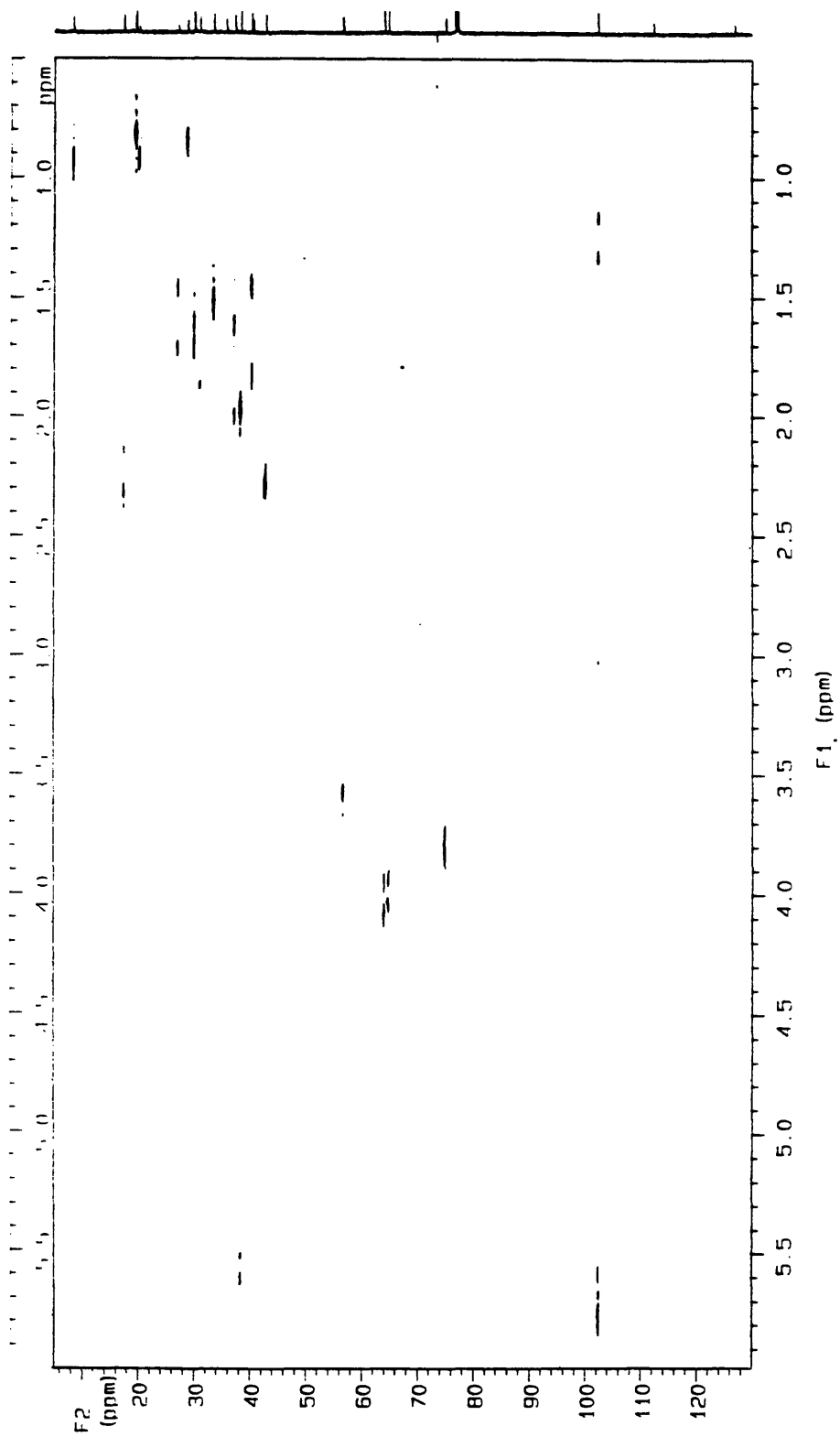


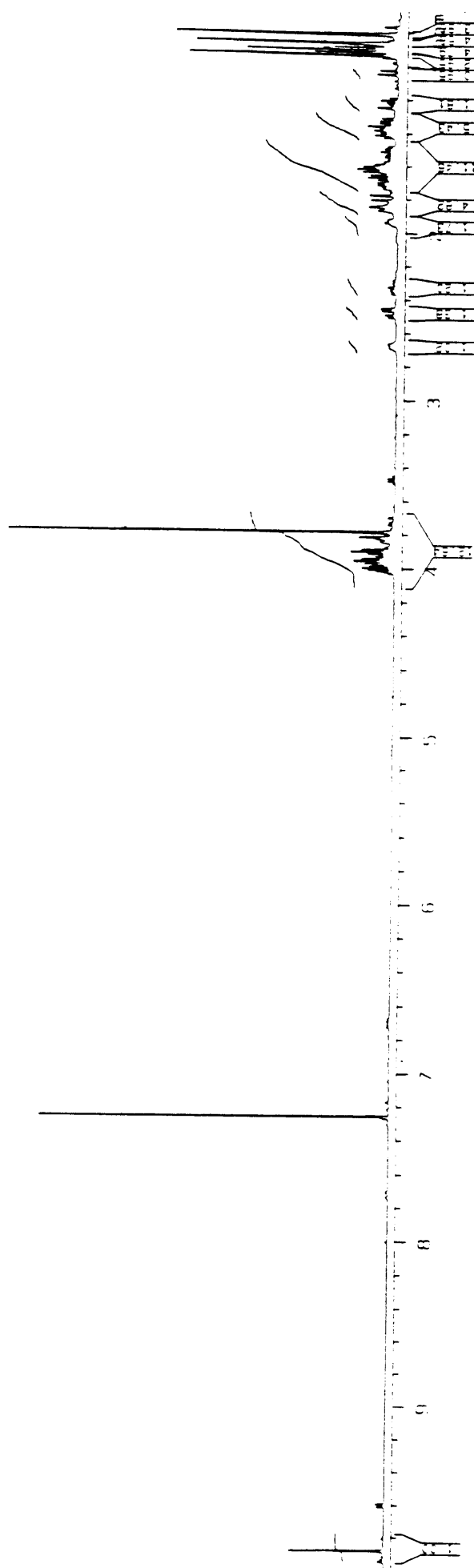
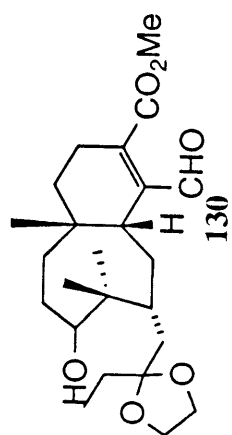


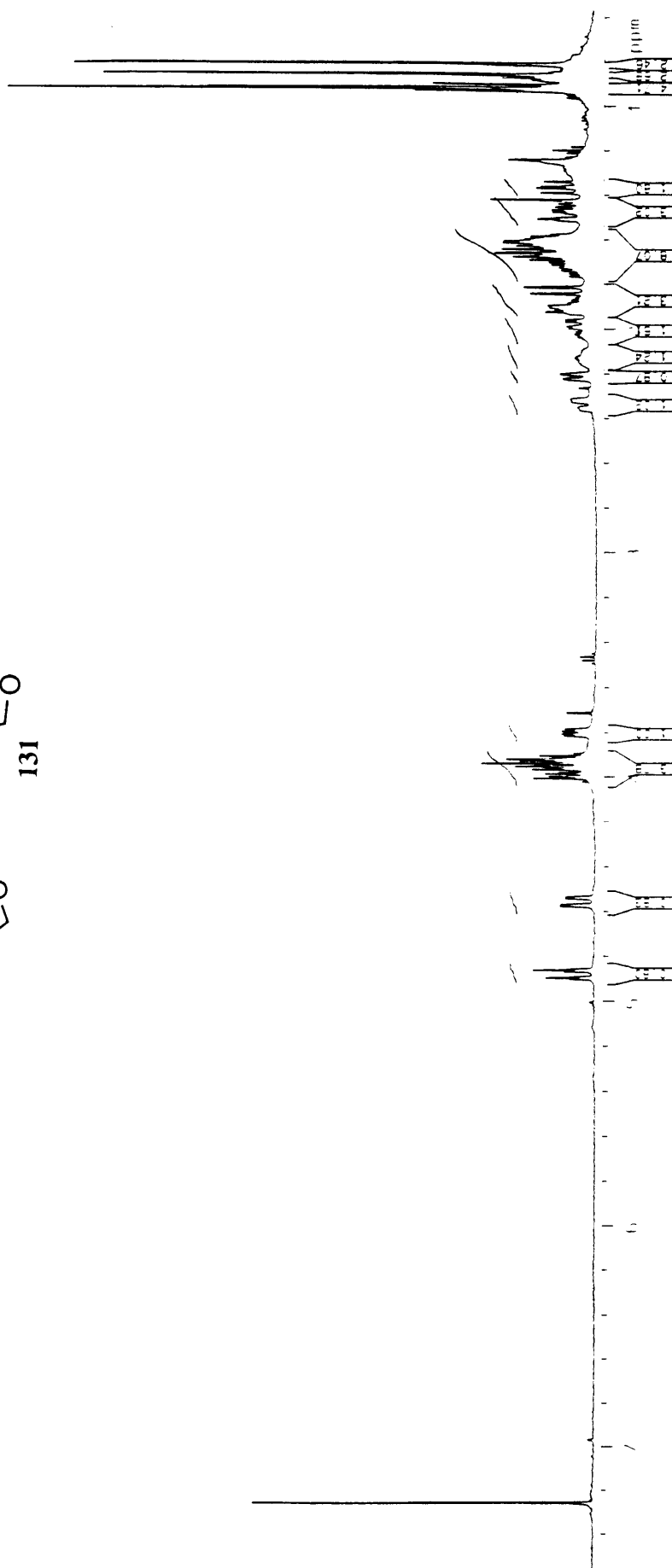
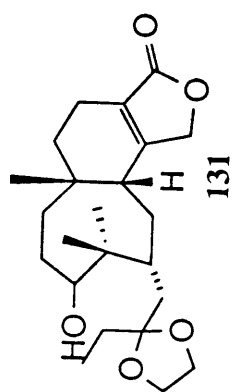


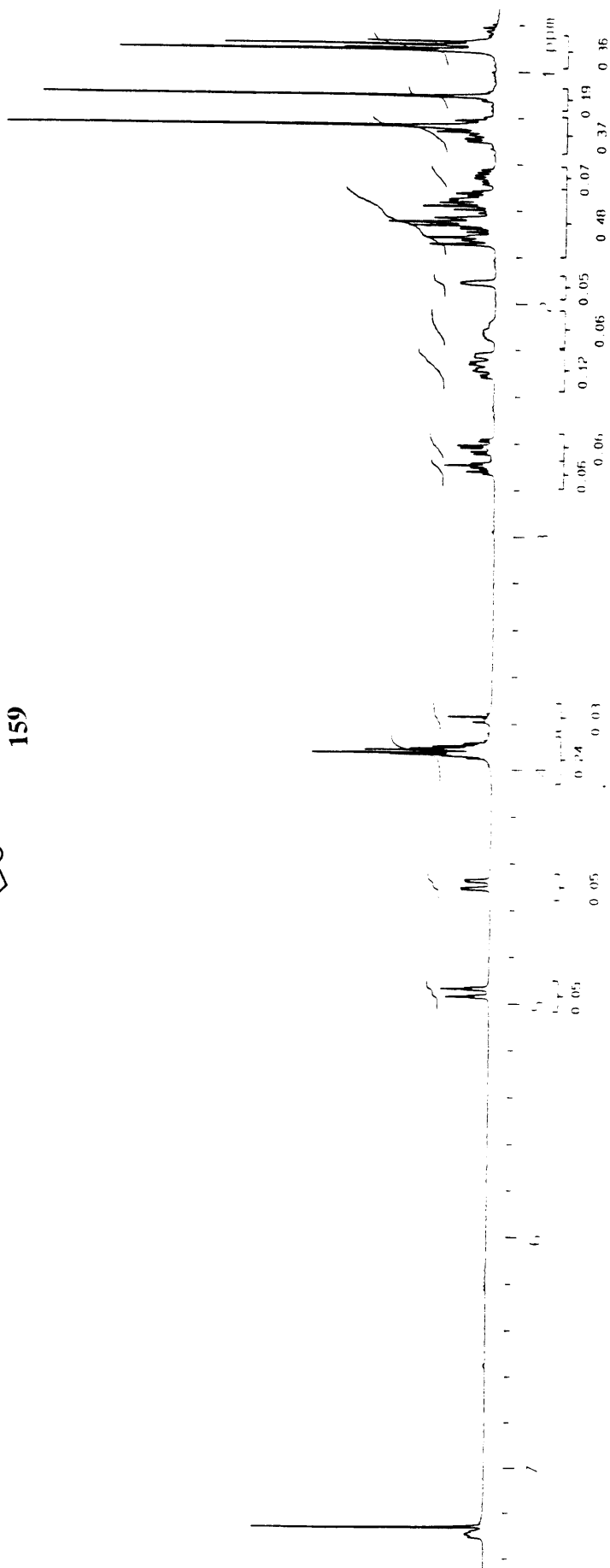
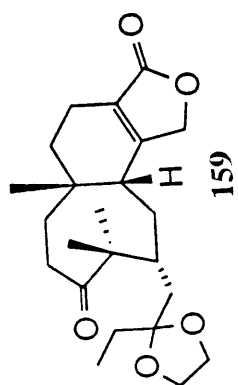


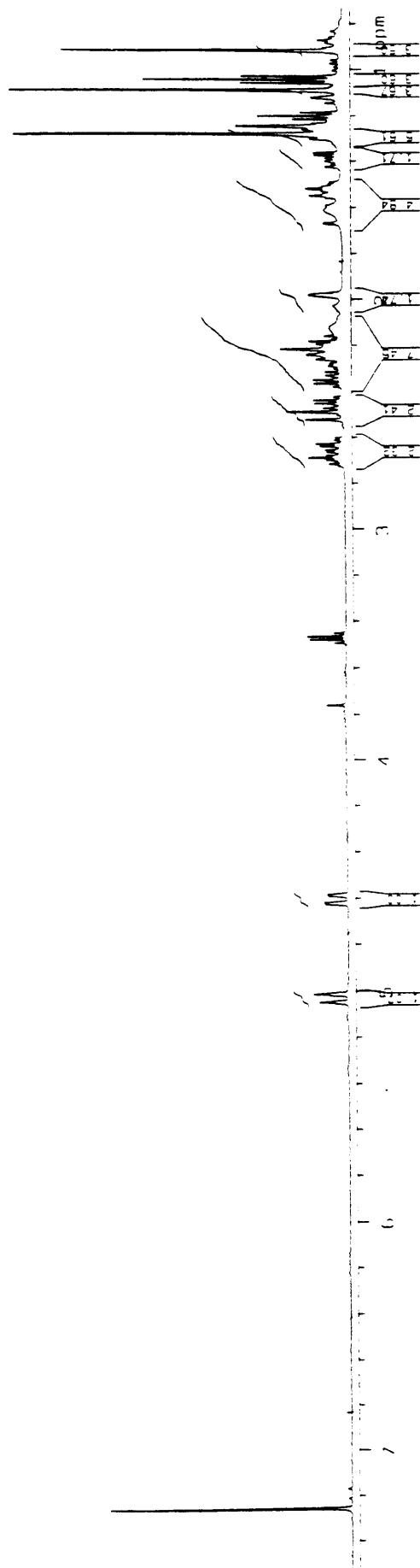
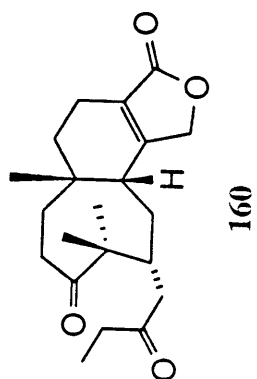
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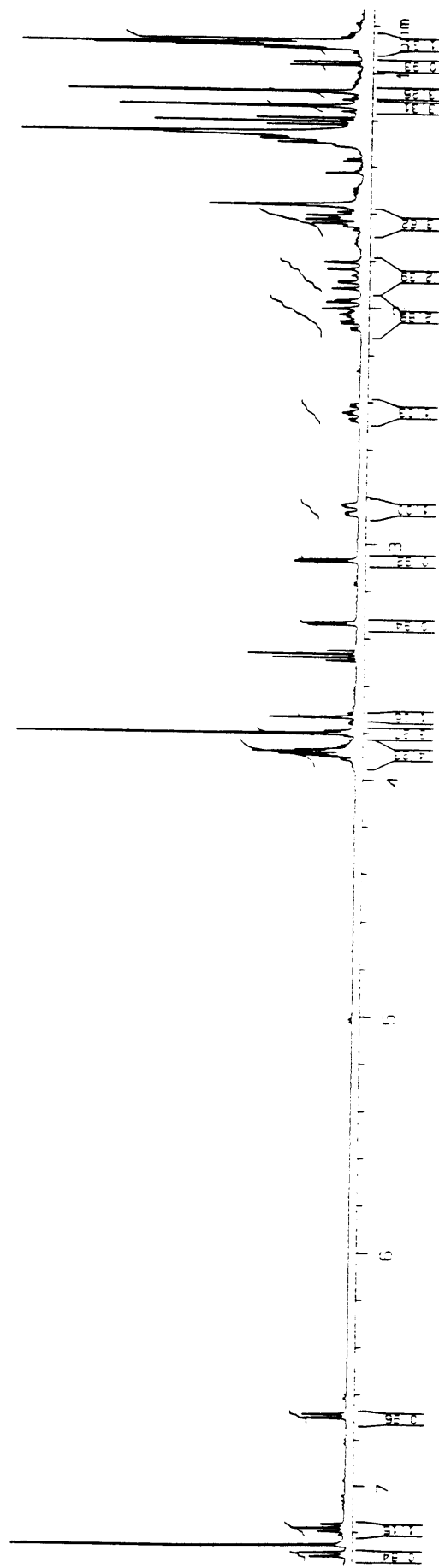
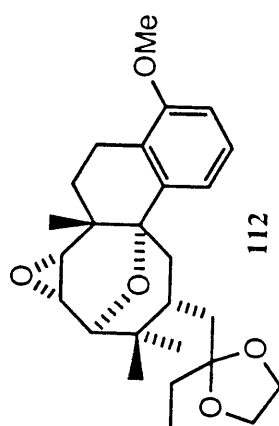


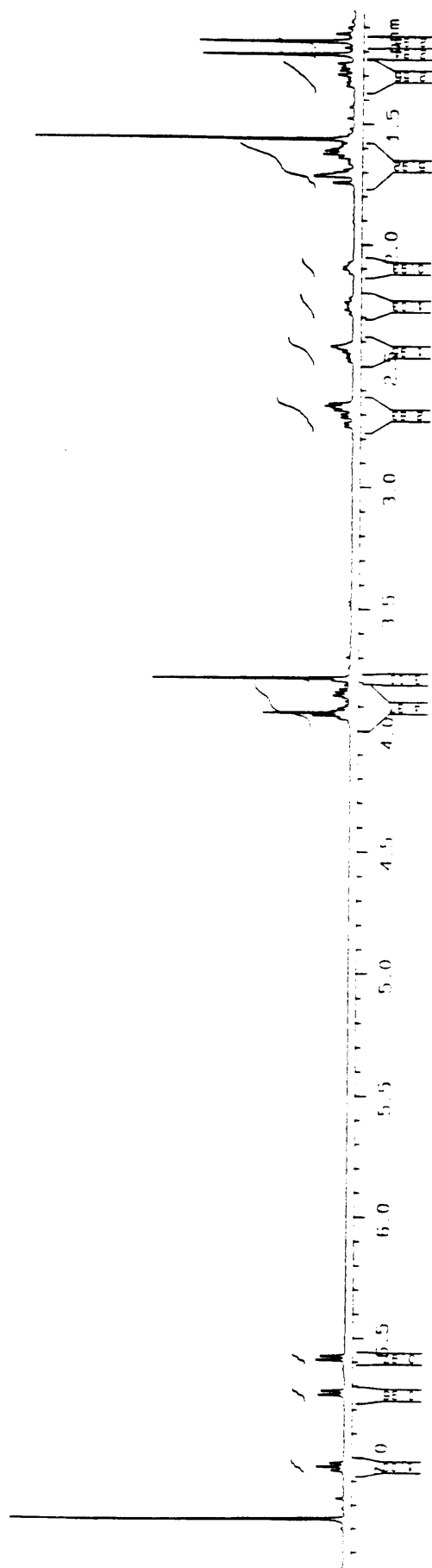
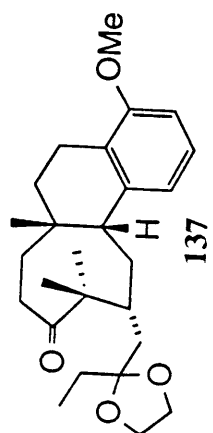


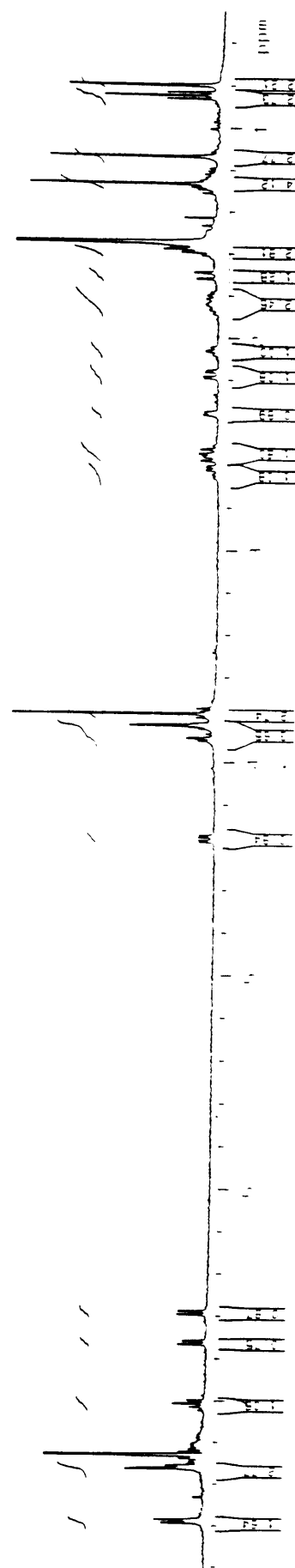
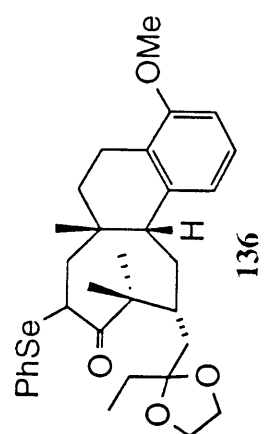


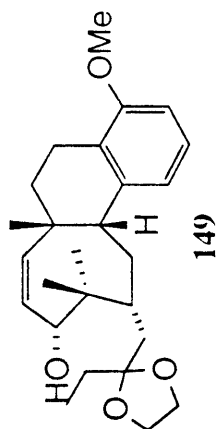




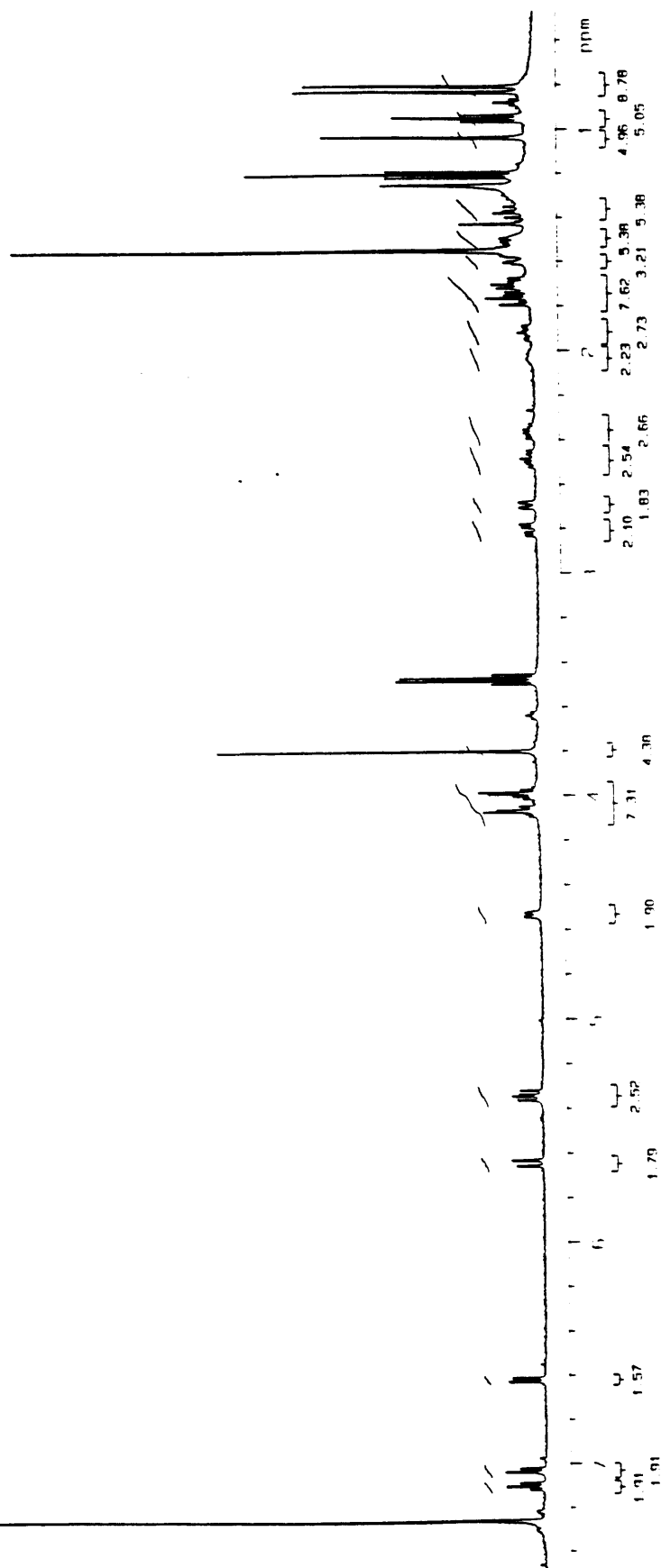


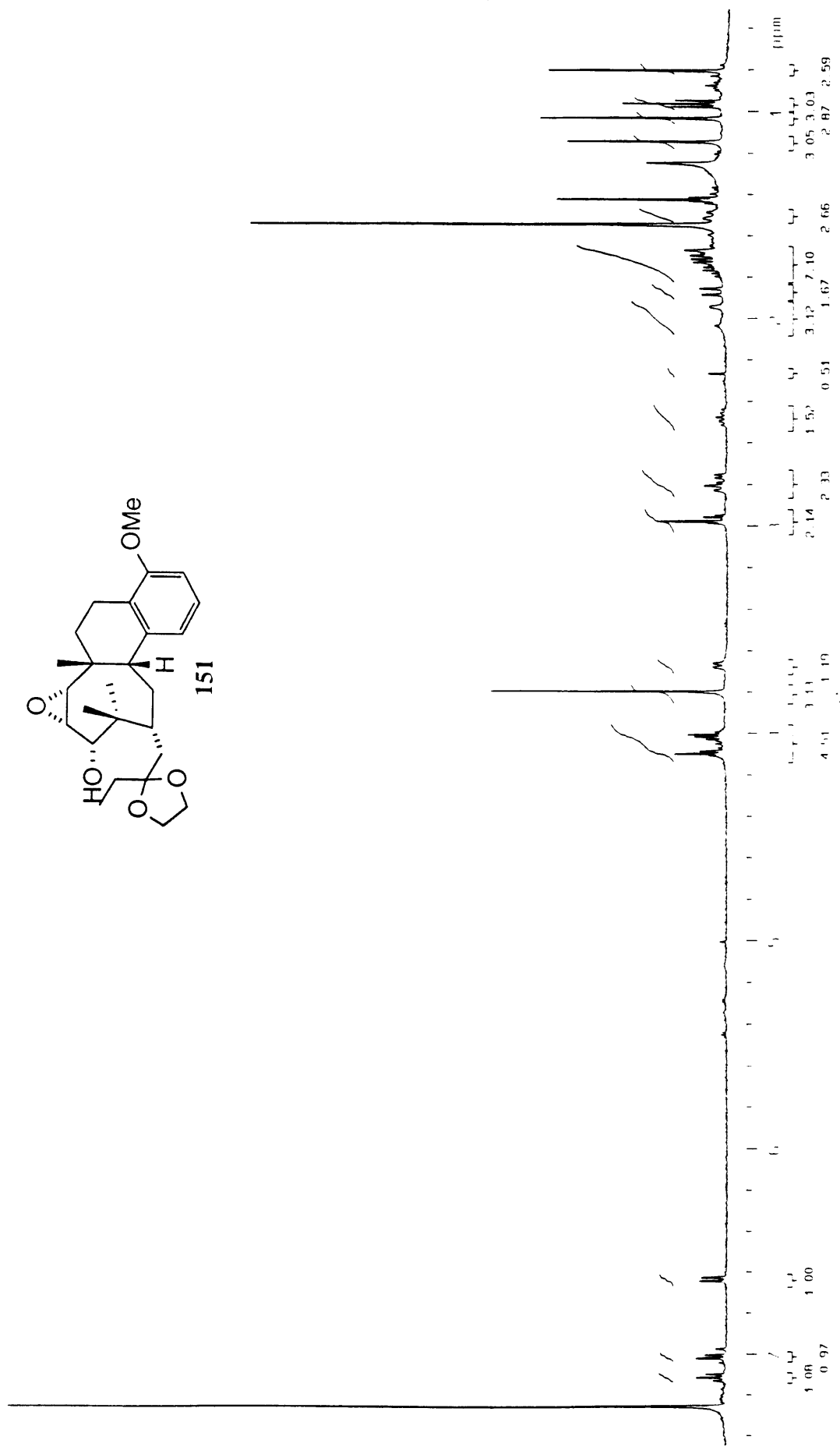


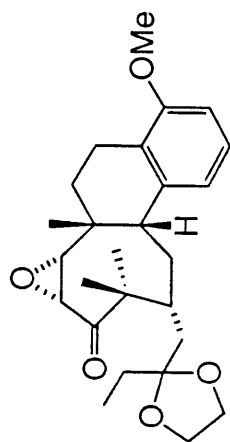




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